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Induced Pluripotent Stem Cells: To Model, To Treat

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Abstract

The development of the ability to convert somatic cells into induced pluripotent stem cells (iPSCs) through expression of a small combination of transcription factors is a major breakthrough in the field of stem cell research. It has raised the possibilities of providing personalized cells for the study and treatment of numerous human diseases. In recent years, iPSCs have been derived from patients of a large variety of disorders. Here, the progresses that has been made in establishing iPSC-based disease models and the potentials of iPSC technology for personalized medicine, drug discovery and cell therapy are reviewed. The challenges from iPSC technology are also briefly discussed.

Introduction

In 2006, the groundbreaking work by Takahashi and Yamanaka showed that retroviral expression of a set of four genes (*Oct4*, *Sox2*, *Klf4* and *c-Myc*) converted somatic cells into a pluripotent state. Similar to the embryonic stem cells (ESCs), these cells exhibit the ability to self-renew endlessly and give rise to a multitude of cell types [1]. The remarkable progress in reprogramming technology over the past few years has facilitated the generation of iPSCs. iPSCs have been derived at increased efficiencies from several easily accessible human cell types, including blood cells, keratinocytes and dermal fibroblasts [2-5]. The advances in iPSC technology has now opened new windows for developing human disease models, drug screening, as well as for providing a continuous autologous cell sources with potential for use in cell therapies [2,5-13].

Here, the increasing efforts in using iPSCs for human disease modeling and potentials of disease-specific iPSCs as platforms for disease mechanism discovery and drug screening are reviewed. In light of the prospects for iPSCs as a source of cell replacement in degenerative diseases, recent studies using iPSC-based therapy are also enumerated. Finally, the challenges for clinical applications of iPSC technology are also brought up to attentions.

iPSCs in Disease Modeling

One of the most promising features of somatic cell reprogramming is the possibility of using iPSCs to model human diseases in order to recapitulate their development, pathology, and pharmacological responsiveness. The ability to generate induced pluripotent cells from patients suffered from diseases of known and suspected aetiologies can allow people to obtain genetically matched cell types in unlimited quantity. In the past few years, great efforts have been put to generate iPSC lines from patients with a wide range of genetically inherited as well as sporadic diseases [2-4,14-16]. In most of these studies, iPSCs from patients have been successfully differentiated to the cell types relevant to the disorders. To date, there are many studies showing that patient-specific iPSCs do exhibit relevant disease features.

A hallmark of these studies was the generation of iPSCs from patients with spinal muscular atrophy (SMA), an inherited neurodegenerative disorder that affects motor neurons [17]. The disease was recapitulated by culturing motor neurons derived from SMA-iPSCs and demonstrating the degeneration of these motor neurons over time [17]. In another study, the enlargement of cardiomyocytes derived from iPSCs from patients with LEOPARD syndrome may reflect the hypertrophic cardiomyopathy associated with this disease [18]. In patients of Long QT syndrome (LQTS), QT intervals are increased on electrocardiography. The differentiated cardiomyocytes produced from iPSCs from these patients showed prolongation of action potential duration in electrophysiological assays [19,20]. LQTS-derived cells also showed marked arrhythmogenicity, characterized by early-after depolarizations and triggered arrhythmias [19]. In the studies of the disease phenotypes of iPSCs derived from Hutchinson-Gilford progeria patients, the premature senescence of the differentiated smooth muscle cells was found, indicating that vascular defects of patients can also be observed *in vitro* [21,22]. The iPSCs from patients of familial dysautonomia-derived exhibit decreased neurogenic differentiation and migration behaviours, compared with control iPSCs [7,23]. The tissue-specific alteration of gene splicing of the *IKBKAP* gene was also found in this study [23]. It thus provided the clues into the tissue specific pathology of familial dysautonomia. Similarly, iPSCs have been used to model many other neurological disorders [8,9,16,24-29], including schizophrenia [30-32], Alzheimer's disease [33], amyotrophic lateral sclerosis [34], Rett syndrome [35-38], fragile X syndrome [39,40], X-linked adrenoleukodystrophy [41] and spinocerebellar ataxia [6]. These studies provide clear evidences that disease modelling using iPSC technology could be feasible.

iPSCs in Pharmaceutical and Cell Therapy

The iPSC technology not only allows us to study the pathological progression of the diseases, but also provides a new platform for testing the effects of drug treatment [3,12,13,42]. The identification of signal pathways or drugs that could affect the disease process will be the ultimate goal of iPSC technology. In the above mentioned study,

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the loss of neurons differentiated from iPSCs of SMA patients was ameliorated by treatment with small-molecule candidates that reverse disease features in other neuronal culture assays [17]. Likewise, the LQTS iPSC-derived cardiac-tissue model was used to evaluate the potency of existing and novel pharmacological agents that may either aggravate (potassium-channel blockers) or ameliorate (calcium-channel blockers, K(ATP)-channel openers and late sodium-channel blockers) the disease phenotype [19]. Key cellular and molecular elements of the schizophrenia phenotypes were ameliorated following treatment of schizophrenia iPSC derived neurons with the antipsychotic loxapine [31]. These studies illustrate the ability of iPSC technology to identify potential therapeutic agents. As such, it represents an inspiring paradigm for optimizing patient care (personalized medicine) and the development of drug screening.

Another exciting aspect of iPSC technology is the possibility of generating autologous cells for cell therapy. One of the excellent examples for advances in the development of iPSC-based therapies is related to Fanconi anemia (FA) [43]. The iPSCs derived from patients with FA (FA-iPSCs) can be generated and maintained only after correction of the FA-related gene. The study clearly showed that, after the introduction of the proper FA-related gene, FA-iPSCs could be differentiated into the hematopoietic lineage [43]. This study provided a model for the derivation of iPSCs from a patient, correction of the disease-associated mutation, and eventual provision of a continuous source for cell therapy. In another study, Kazuki et al. [44] corrected the defective gene in iPSCs derived from a patient with Duchenne muscular dystrophy (DMD-iPSCs) using human artificial chromosomes (HAC). The study suggested that combination of patient-specific iPSCs and HAC-containing defective genes represents a powerful tool for gene and cell therapies. With regards to transplantation of iPSCs for therapeutic regeneration, the most compelling study so far showed that haematopoietic cells derived from iPSCs can reduce the blood cell phenotype in a humanized mouse model of sickle cell anemia [45]. The Parkinson's disease is characterized by the slow but steady decline in dopaminergic neurons. Wernig et al. [46] demonstrated that iPSCs could be induced to differentiate into dopamine neurons of midbrain character and were able to improve behavior in a rat model of Parkinson's disease upon transplantation into the adult brain. Hargus et al. [11] developed the cell-based treatment approach by deriving iPSCs from Parkinson's disease patients, differentiating these into dopaminergic neurons, and then transplanting the cells into the brains of rats with Parkinson's disease. The iPSCs have also been utilized for treatment of stroke [47], hepatic failure [48] and myocardial infarction [49] in animal models.

Taken together, these studies provide strong support for the roles of iPSCs in both pharmaceutical and cell therapies of human diseases. These recent developments have brought the dreams of clinical applications of iPSCs much closer to reality.

Conclusion

Although studies in the field of iPSCs have been advanced dramatically, many issues still need to be addressed and improved in terms of the cell reprogramming, the differentiation potential of cells, and the future clinical application of iPSC technology [2,5,12,25,50]. The challenges especially involve the safety concerns regarding the generation of iPSCs and the introduction of iPSC-derived cells into patients. The iPSC technology has been proven to be a powerful approach for *in vitro* studies, it will hold enormous prospects for disease modeling, personalized medicine, drug screening and cell-based therapies, provided that all these fundamental challenges from iPSC technology are given due attention and priority.

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