

Is Human-induced Pluripotent Stem Cell the Best Optimal?

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Abstract

Objective: Since the advent of induced pluripotent stem cell (iPSC) technology a decade ago, enormous progress has been made in stem cell biology and regenerative medicine. Human iPSCs have been widely used for disease modeling, drug discovery, and cell therapy development. In this review, we discuss the progress in applications of iPSC technology that are particularly relevant to drug discovery and regenerative medicine, and consider the remaining challenges and the emerging opportunities in the field.

Data Sources: Articles in this review were searched from PubMed database from January 2014 to December 2017.

Study Selection: Original articles about iPSCs and cardiovascular diseases were included and analyzed.

Results: iPSC holds great promises for human disease modeling, drug discovery, and stem cell-based therapy, and this potential is only beginning to be realized. However, several important issues remain to be addressed.

Conclusions: The recent availability of human cardiomyocytes derived from iPSCs opens new opportunities to build *in vitro* models of cardiac disease, screening for new drugs and patient-specific cardiac therapy.

Key words: Cardiovascular Diseases; Embryonic Stem Cells; Induced Pluripotent Stem Cells

INTRODUCTION

Cardiovascular diseases (CVDs) are the most common causes of morbidity and mortality worldwide, which negatively affect public health.^[1] Endothelial damage is regarded as a key early event in the development of atherosclerosis, which contributes to the myocardial infarction.^[2] Human umbilical vein endothelial cells (ECs) are widely used for studying the functions and pathology states of ECs.^[3] However, they are not patient specific and could not show the individual differences observed among patients when used for diseases modeling and drugs screening. Genetically matched stem cell-derived ECs can be patient specific and disease specific; they are ideal cell resources for studying the pathophysiology processes of CVDs and regenerating the blood vessels for purposes of personalized medicine.^[4,5] For these reasons, patient- and disease-specific stem cell-derived ECs and cardiomyocytes would be good candidates for preclinical drug discovery and regenerative therapy for CVDs.^[6-8]

Pluripotent stem cells (PSCs) are capable of unlimited self-renewal and ability to form any somatic cell types. PSCs can be derived from embryonic cells and adult somatic cells. Somatic cells can be reprogrammed to the pluripotent state

by a number of methods such as cell fusion^[9,10] and somatic cell nuclear transfer.^[11,12] However, both approaches are low efficiency and limited by ethic issues, which prevented their widely use under the clinical settings. In 2006, Takahashi and Yamanaka successfully cultured mouse embryonic and adult fibroblast-derived human-induced PSCs (iPSCs) by ectopic overexpression of OSKM (OCT4/SOX2/C-MYC/KLF4).^[13] It is a promising breakthrough and provides a new opportunity in the regenerative medicine. After that, many researchers also successively obtained the iPSCs using the same approach.^[14-16] Because iPSCs have no ethical issues and could derive from patient- and disease-specific somatic cells, they are widely used in various fields, especially in the cardiovascular field. Despite the subtle differences in epigenetic modifications and gene expression signatures, iPSCs are generally similar to embryonic stem cells (ESCs)

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in the capacity of unlimited self-renewal and differentiation to any somatic cells.^[17,18] iPSCs are very similar to ESCs not only in cell morphology, growth characteristics, and stem cell marker expression but also in DNA methylation mode, gene expression profile, chromatin status, and chimeric animals.^[4-7]

OPTIMIZING THE REPROGRAMMING CONDITIONS

The discovery of iPSCs provided new approaches for cell replacement therapy, as well as new ways for drug screening and disease modeling. However, the undefined mechanism and relatively low efficiency of reprogramming have limited the applications of iPSCs. Therefore, it is vital to further optimize the reprogramming conditions. To enhance reprogramming efficiency or replace reprogramming genes, microRNAs (miRNAs) and small-molecule compounds have been explored for cell reprogramming. For example, miR-291-3p, miR-294, and miR-295 can replace c-myc and generate homogeneous populations of iPSCs; inhibition of let-7 miRNA enhances the expression of target genes c-myc and Lin-28 to promote cell reprogramming.^[19,20] There is also evidence that the miRNA302/367 cluster can reprogram somatic cells into iPSCs without the requirement for exogenous transcription factors, although the reprogramming efficiency is lower.^[21]

Small-molecule compounds can replace some of the reprogramming genes or modulate epigenetic state to enable or improve reprogramming efficiency.^[22-25] Via high-throughput screening, an inhibitor of transforming growth factor beta (TGF- β) signaling was identified, which can replace Sox2 and induce Nanog expression.^[23] Inhibitors of the TGF- β and MEK pathways also facilitate mesenchymal-to-epithelial transition which is a required step in iPSC reprogramming.^[26] During the reprogramming process, a combination of several chemical compounds can replace Sox2 and c-myc.^[27] Oct4-activating compounds were also recently identified.^[24] Histone modifications, including acetylation and methylation, play an important role in epigenetic changes in cell reprogramming, and the small molecules that regulate histone modifications have been shown to significantly enhance reprogramming efficiency.^[28] Valproic acid (VPA), a histone deacetylase (HDAC) inhibitor, increases the percentage of Oct4⁺ cells generated during reprogramming.^[22] Tranylcypromine hydrochloride (TCP), an inhibitor of lysine-specific demethylase, also improves reprogramming efficiency.^[23] A recent study demonstrated that it is feasible to generate iPSCs using small molecules alone, which represents significant progress in cell reprogramming technology.^[29]

Biophysical factors such as the mechanical properties and micro/nanostructure of cell-adhesion substrates may also play a role in cell reprogramming. For example, micro/nanotopography can regulate cell and nucleus shape, modulate the epigenetic state, and replace biochemical factors (i.e., VPA and TCP) to enhance cell reprogramming into iPSCs.^[30] Interestingly, cell reprogramming with OSKM

factors can be performed in suspension culture under adherence- and matrix-free conditions, which suggests that OSKM factors are sufficient to reprogram cells without the input of cell adhesion-induced signaling. How cell reprogramming efficiency is modulated by cell adhesion needs further studies.^[31]

INDUCED PLURIPOTENT STEM CELL-GENERATED CARDIOMYOCYTES AND DISEASE MODELING

To mimic the CVD, researchers had used many methods to differentiate iPSCs into functional cardiomyocytes; the three most frequently used methods are as follows: (1) coculture with mouse visceral endoderm-like (END-2) stromal cells, (2) spontaneous embryoid body differentiation in suspension, and (3) two-dimensional (2D) monolayer differentiation.^[32] Now, the iPSC-generated cardiomyocyte (iPSC-CM) has become the ideal model to study the etiology and develop therapeutic strategies for long Q-T syndrome,^[33] catecholaminergic polymorphic ventricular tachycardia,^[34] arrhythmogenic right ventricular cardiomyopathy,^[35] familial hypertrophic cardiomyopathy,^[36] and familial dilated cardiomyopathy.^[37]

MATURITY AND PURITY OF INDUCED PLURIPOTENT STEM CELL-GENERATED CARDIOMYOCYTES

Improving maturity in iPSC-CMs remains one of the major priorities of the field, since phenotypic immaturity limits their ability to successfully model critical aspects of cardiac disorders including adult-onset diseases.^[38] Many functional features of iPSC-CMs, such as their cell morphology, electrophysiological characteristics, sarcomere organization and contraction force, are underdeveloped compared with adult cardiomyocytes.^[39,40] Channelopathies are among the cardiac diseases that suffer least from these limitations, since most relevant channels for the generation of the cardiac action potential are expressed in iPSC-CMs. However, it is noteworthy that although the efficiency of differentiation protocols has undergone a multifold increase over recent years as a result of culture condition optimization, this has not been paralleled by improvements in maturation of the electrophysiological properties of iPSC-CMs: resting membrane potential is depolarized, and upstroke velocity and ion channel expression remain low in comparison with adult cardiomyocytes.^[38,41] Most of these differentiation protocols result in mixed populations of ventricular-, atrial-, and nodal-like subtypes, with ventricular CMs being the most represented. Some recent studies have succeeded in directing PSC differentiation toward atrial and pacemaker subtypes; however, their application for studying molecular mechanisms related to disease is still under investigation.

Since their discovery in 2006, iPSCs have evolved rapidly and ushered in an exciting new era for the field of disease modeling, as well as the fields of drug discovery and regenerative medicine.^[13] The advantages, comparing with traditional methods, include their human origin, easy

accessibility, expandability, ability to give rise to almost any cell types desired, avoidance of ethical concerns associated with human ESCs, and the potential to develop personalized medicine using patient-specific iPSCs.

Furthermore, recent advances in gene-editing technologies, especially the CRISPR-Cas9 technology and 3D technology, are enabling the rapid generation of genetically defined human iPSC-based disease models.

INDUCED PLURIPOTENT STEM CELL-BASED DRUG SCREENING

One of the fundamental applications of iPSC cardiac disease models is to develop the treatments as achieved in some neurodegenerative disorders.^[42] This approach is highly dependent on understanding the molecular mechanisms underlying the disease, as well as on the sensitivity of the readout in the assay that is used for detecting the abnormal phenotype. Testing a limited number of candidate drugs based on underlying disease mechanisms is already proving the fastest way to move forward to clinical application, since it is based on repurposing previously approved compounds for a new disease.^[43] As an alternative to repurposing, iPSC-CMs can be used as a platform for high-throughput drug testing,^[44] which is most valuable to pharmaceutical companies looking for new drug and disease targets since they often have technologies for automated measurements.

In addition to drug screening and drug development, iPSC-CMs are demonstrated their value in revealing cardiotoxic effects. These cells are proving a valuable tool to identify electrophysiological and transcriptional changes related to HDAC inhibitor-mediated cardiotoxicity.^[45]

INDUCED PLURIPOTENT STEM CELL-BASED REGENERATIVE MEDICINE

Heart failure is one of the most common causes of death worldwide, and cardiac regeneration using iPSCs is expected to be a useful tool for the treatment. Using a guinea pig model, Shiba *et al.*^[46] reported that transplanted cardiac myocytes were able to form gap junctions with the surrounding host myocardium and achieve 1:1 host-graft coupling. Cotransplantation of noncardiac myocytes may enhance the trophic effects.^[47] It was reported that transplanted human iPSC-CMs can engraft and form myocardium in rodents.^[32,48,49] However, the survival of the transplanted cardiac myocytes are limited, compromising efficient regeneration of the injured myocardium. Hydrogel composed mainly of laminin, matrigel, and a pro-survival cocktail (including insulin-like growth factor 1 [IGF-1] and cyclosporine A) along with heat shock pretreatment improved the survival of the transplanted cells through antiapoptotic effects.^[32,34,35,50-52] We recently reported that the engraftability of iPSC-CMs differs depending on the maturation stage.^[53]

To improve the survival of transplanted cells, cardiac myocyte sheets and aggregates of cardiac myocytes have

been used.^[51,52] Epicardial transplantation using stacked cell sheets was also reported to improve the cardiac function.^[54] Zimmermann *et al.*^[55] reported a technology to generate engineered heart tissue that generates contractile force using neonatal rat cardiac myocytes. The engineered heart tissues engrafted efficiently after transplantation into immunosuppressed infarcted rat hearts and improved the cardiac function. This technology can be applied to cardiac myocytes derived from iPSCs.^[56,57] Based on murine models, larger animal models have been reported more recently. Transplantation studies using a monkey model revealed that iPSC-CMs were able to engraft in the infarcted hearts of monkeys treated with immunosuppressive agents.^[58] Kawamura *et al.*^[59] reported the transplantation of cell sheets composed of cardiac myocytes derived from human iPSCs using a pig model of myocardial infarction. Intramyocardial transplantation of cardiac myocytes along with smooth muscle cells and ECs all derived from iPSCs, with a 3D fibrin patch containing IGF-1 being shown to increase the cardiac function in another porcine model of acute myocardial infarction.^[60] New evidence indicates that the outcomes of cell therapies will benefit from donor matching. In allogeneic transplantation experiments, cardiac myocytes derived from monkey iPSCs with major histocompatibility complex homozygosity were shown to engraft into infarcted hearts and improve the cardiac function of heterozygous major histocompatibility complex-matched monkeys.^[61] The immune response of the heterozygous major histocompatibility complex monkeys was favorable when transplantation involved cardiac myocytes derived from homozygous major histocompatibility complex-matched monkey iPSCs than from monkeys without identical major histocompatibility complex alleles.^[62] These findings support the clinical rationale of allogeneic transplantation using major histocompatibility complex homozygous iPSCs. Nevertheless, ventricular arrhythmias may occur after the transplantation of cardiac cells.^[58,61] The transplantation of immature or dedifferentiated cells can result in heterogeneity of repolarization, leading to reentry and triggered activity. Paracrine factors secreted from the graft cells may also cause electrophysiological changes, resulting in arrhythmia generation through increased automaticity, triggered activity, and reentry.^[63,64] The first clinical transplantation of human ESC-derived cardiac progenitors was reported by Menasché *et al.*^[65,66] They successfully transplanted cardiac progenitor-loaded fibrin patches into the hearts of patients with advanced ischemic heart failure. Considering the similarity between cardiac myocytes derived from human ESCs and those derived from iPSCs, a platform developed using human ESCs should be applicable to human iPSCs.

CONCLUSIONS

The recent availability of human cardiomyocytes derived from iPSCs opens new opportunities to build *in vitro* models of cardiac disease, screening for new drugs and patient-specific cardiac therapy.

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Conflicts of interest

There are no conflicts of interest.

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人诱导多能干细胞是否是最优的选择

摘要

目的：自十多年前诱导性多能干细胞（iPSC）技术问世以来，干细胞生物学和再生医学取得了巨大的进展。人类iPSC已广泛用于疾病建模，药物发现和细胞治疗。在这篇综述中，我们将讨论与药物发现和再生医学相关的iPSC技术应用的进展，并考虑在该领域中面临的挑战和新兴的机会。

数据来源：本评价文章均从2014年1月至2017年12月从PubMed数据库中搜索。

研究选择：包括并分析关于iPSC和心血管疾病的原始文章。

结果：iPSC对人类疾病模型，药物发现和基于干细胞的治疗抱有很好的前景，这种潜力才刚刚开始实现。但是，有几个重要问题仍有待解决。

结论：最近获得来自iPSC的人心肌细胞为开发心脏疾病的体外模型，筛选新药物和患者特异性心脏治疗开辟了新的机会。
