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Human Induced Pluripotent Stem Cell Models of Inherited Cardiomyopathies

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Abstract

Purpose of the review—This article provides an overview of the latest advances on *in vitro* modeling of inherited cardiomyopathies using human induced pluripotent stem cells (iPSCs).

Recent findings—Inherited cardiomyopathies have been recently modeled by generating iPSCs from patients harboring mutations in genes associated with the pathogenesis of HCM, DCM, and ARVC/D.

Summary—Patient-specific iPSCs and their differentiated cardiomyocytes (iPSC-CMs) now provide a novel model to study the underlying molecular mechanism of the pathogenesis of familial cardiomyopathies as well as for *in vitro* drug screening and drug discovery.

Keywords

induced pluripotent stem cells; inherited cardiomyopathy; hypertrophic cardiomyopathy; dilated cardiomyopathy; arrhythmogenic right ventricular cardiomyopathy

Introduction

Inherited cardiomyopathies are a major cause of morbidity and mortality. In recent years, exciting progress has been made in defining the etiology of inherited cardiomyopathies, including hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), left ventricular non-compaction cardiomyopathy (LVNC), and arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) [1]. To date, numerous mutations in more than 50 genes that are implicated in the pathogenesis of inherited cardiomyopathies have been discovered [2] (Figure 1). The clinical course of these disease-causing mutations is remarkably variable, ranging from early severe phenotype and sudden cardiac death in

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Conflict of interest

None

adolescents to lifelong, asymptomatic, mutation-carrier status. Although the molecular analysis efforts have revealed important insights regarding the role of genetics in cardiomyopathies, the underlying mechanisms of HCM, DCM, LVNC, and ARVC/D remain unclear. An improved understanding of the pathological mechanisms involved in inherited cardiomyopathies could potentially lead to novel therapies.

The emergence of human pluripotent stem cells (PSCs), which include both human embryonic stem cells (ESCs) [3] and human induced pluripotent stem cells (iPSCs) [4], and the rapidly advancing technology and differentiation protocols associated with them, have made it possible to quickly interrogate the effects of genetic modifications. The ability to generate patient-specific iPSCs provides new opportunities to further understand disease pathogenesis and to develop new therapies. In this review, we will summarize recent advances in iPSC technology to study the molecular mechanisms underlying the pathogenesis of inherited cardiomyopathies.

Familial Hypertrophic Cardiomyopathy

Familial hypertrophic cardiomyopathy (HCM) is the most common monogenically inherited form of heart disease, predominantly caused by mutations in sarcomere protein genes [5]. Interestingly, most of these genes encode sarcomeric proteins, such as cardiac muscle β -myosin heavy chain (*MYH7*), cardiac muscle troponin T (*TNNT2*), and cardiac myosin-binding protein C (*MYBPC3*). However, the molecular events that link the sarcomere mutation to the development of the clinical phenotype of HCM are still unclear. In a recent study by Lan et. al. [6]*, human induced pluripotent stem cell-derived cardiomyocytes (iPSC-CMs) were generated from a family carrying an autosomal dominant missense mutation on exon 18 of the *MYH7* gene that encodes for an Arginine-to-Histidine substitution at amino acid position 663 (Arg663His) [6]. The study showed for the first time that iPSC-CMs can recapitulate the HCM disease phenotype at the single-cell level, including cellular hypertrophy, calcineurin/nuclear factor of activated T-cells (NFAT) activation, upregulation of hypertrophic transcription factors, and arrhythmia. The study also demonstrated that elevation in intracellular calcium ($[Ca^{2+}]_i$) preceded the presentation of other phenotypic abnormalities, suggesting that dysregulation of Ca^{2+} cycling is a central mechanism for pathogenesis of the disease. Importantly, cellular hypertrophy and Ca^{2+} cycling abnormalities can be prevented with calcium channel blockers such as verapamil, diltiazem, and nifedipine. These findings validated iPSC technology as a novel method to understand how sarcomeric mutations can cause the development of cardiac hypertrophy and arrhythmia, and to potentially identify new therapeutic targets for the disease. Furthermore, while iPSCs can be used to complement existing zebrafish [7] and mouse [8] models of hypertrophic cardiomyopathy, the main advantage here is that beating human heart cells are being studied directly.

Familial Dilated Cardiomyopathy (DCM)

Dilated cardiomyopathy (DCM) is a clinical disease entity defined by left ventricular dilatation and impaired systolic function. DCM is composed of a heterogeneous group of diseases with different etiologies, with familial disease being responsible for one third to

half of the cases [9]. Familial DCM is a leading cause of heart failure and is caused by mutations in at least 40 different individual genes of diverse ontologies. DCM was first modeled by Sun et al. using iPSCs from patients carrying a heterozygous mutation in the cardiac troponin T (TNNT2), namely p.R173W [10]*. In this model, an increased heterogeneous sarcomeric organization and a pronounced punctate distribution of sarcomeric α -actinin were observed. Individual DCM iPSC-CMs also exhibited altered Ca^{2+} handling compared to iPSC-CMs from control individuals. In addition, β -adrenergic stimulation (with norepinephrine) increased the number of DCM iPSC-CMs with abnormal sarcomeric α -actinin distribution, compromised cellular contractility, and induced failure of spontaneous contraction.

Patient-specific DCM iPSC lines have also been generated from a patient with a novel heterozygous mutation of p.A285V codon conversion on exon 4 of the desmin (*DES*) [11], as well as from an autosomal dominant nonsense mutation (p.R225X) in exon 4 of the lamin A/C (*LMNA*) gene found in a Chinese family with familial DCM spanning 3 generations [12]. The *DES* mutation was associated with diffuse abnormal *DES* aggregations in DCM iPSC-CMs [11], whereas the *LMNA* mutation was shown to accelerate nuclear senescence and apoptosis of iPSC-CMs under electrical stimulation, which was rescued by therapeutic blockade of stress-related ERK1/2 pathway [12]. Taken together, these studies demonstrated that iPSC-CM recapitulated certain aspects of the DCM phenotype *in vitro*, providing a proof-of-concept that iPSCs can be used as a model to study DCM pathogenesis.

Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia (ARVC/D)

ARVC/D is a predominantly genetically determined and heritable form of cardiomyopathy that is characterized pathologically by the replacement of cardiomyocytes by fibrous or fibro-fatty tissue mostly in the right ventricle, and clinically by elevated risks of arrhythmia and sudden cardiac death [13]. Several mutations in several genes encoding components of the cardiac desmosome genes have been linked to ARVC/D, including junction plakoglobin (*JUP*), desmoplakin (*DSP*), plakophilin-2 (*PKP-2*), and desmoglein-2 (*DSG-2*). Three separate studies have examined the effect of mutations in *PKP2* gene in a patient-specific iPSC model of ARVC/D. Kim *et al.* [14] generated iPSCs from two patients with clinical ARVC/D carrying either a homozygous (c.2484C>T) or a heterozygous (c.2013delC) mutation in the *PKP2* gene. Although the investigators observed an abnormal nuclear translocation of junction plakoglobin proteins and very low β -catenin activity in mutant iPSC-CMs from both patients, the disease phenotype was not fully recapitulated in standard culture conditions. In subsequent experiments, the authors discovered that the induction of an adult-like metabolism using an adipogenic cocktail that co-activates the normal PPAR- α -dependent metabolism and abnormal PPAR- γ pathway was imperative to induce the classical signs of ARVC/D, such as intracellular lipid accumulation in iPSC-CMs. These findings suggested that metabolic abnormalities could play a central role in the pathogenesis of ARVC/D. Importantly, this study demonstrated that induction of adult-like metabolism is essential in establishing an adult-onset disease model using patient-specific iPSC-CMs.

The ARVC/D was also modeled by generating iPSCs from patients harboring two novel mutations in the *PKP2* gene, namely c.1841T>C [15]* and c.972InsT/N [16], as well as a

known mutation on the same gene (c.148_151delACAG/N) [16]. All three models showed the mutant iPSC-CMs were prone to lipid accumulation following treatment with various adipogenic stimuli, displaying a functional pro-adipogenic state that is considered to be one of the hallmarks of ARVC/D. In the study by Gepstein and colleagues [16], the authors observed that intracellular lipid droplet accumulation in mutant iPSC-CMs was also shown to be correlated with the degree of the desmosomal abnormalities within the same cell, suggesting a causal link between desmosomal malfunction and lipid accumulation in ARVC/D. Interestingly, the small molecule BIO, a specific inhibitor of GSK-3b, could prevent the effect of the adipogenic stimuli on the mutant cardiomyocytes, implying a possible role of the canonical Wnt pathway in the ARVC/D pathogenesis. Collectively, these studies underscore the unique potential of the iPSC technology for modeling ARVC/D *in vitro*. The iPSCs-CMs that were derived from ARVC/D patients recapitulated, to some extent, the ARVC/D phenotype in the dish, and provided mechanistic insights into early disease pathogenesis.

Left Ventricular Non-Compaction (LVNC) and Restrictive Cardiomyopathy (RCM)

To date, iPSC models of LVNC and RCM have not been reported, although several laboratories are also working actively in these diseases

Using Patient Specific Stem Cell–Derived Cardiomyocytes to Study Proarrhythmia

Cardiac toxicity is a leading cause of regulatory delay in approval and market withdrawal of new pharmaceuticals [17]. Drug-induced blocking of human Ether-à-go-go Related Gene (hERG) potassium channel, which conducts the rapid component of the delayed rectifier potassium current (I_{Kr}), can induce ventricular tachyarrhythmia in the heart known as Torsade de Pointes (TdP) [18]. To minimize cardiac risks associated with drug development, both the pharmaceutical industry and U.S. Food and Drug Administration (FDA) have mandated *in vitro* cardiotoxicity screening early in new chemical entities (NCE) development. Given that the majority of adverse cardiac drug reactions occur in patients with hereditary cardiac disease who are vulnerable to fatal arrhythmias, the recent advances in efficient generation of iPSC-CMs [19] have important implications for drug toxicity screening. Human iPSC technology holds the potential to serve as a human-based model that reflects a variety of genetic backgrounds for both drug development and cardiotoxicity screening. Liang et al. recently assessed the susceptibility of patients from different genetic backgrounds to drug-induced cardiotoxicity in a library of human iPSC-CMs derived from patients with common hereditary cardiac disorders such as familial HCM, familial DCM, and long QT syndrome (LQTS; KCNQ1 mutation) [20]*. Not surprisingly, healthy and diseased individuals exhibited different susceptibilities to cardiotoxic drugs (see Table 1 for the complete list the drugs studied), which were more accurately modeled in iPSC-CMs than the standard cardiotoxicity testing currently performed using Chinese hamster ovary (CHO) or human embryonic kidney (HEK) cells overexpressing hERG. In agreement with these findings, another study suggested that LQTS2 patients (HERG mutation) are at an increased

risk of developing excessive QT prolongation and potentially TdP when exposed to blocking drugs, as indicated by an iPSC-CM based assay [21]. Finally, iPSC-CMs have been used in conjunction with the higher throughput multielectrode array (MEA) platform for screening a panel of cardiovascular drugs such as quinidine, sotalol, verapamil, nifedipine, etc. [22].

Anticipated Advances in the Next Decade

The results from recent studies reviewed here provide proof-of-principle that iPSC-based disease models can generally be expected to reproduce the disease phenotype. These novel iPSC models of inherited cardiomyopathies are being rapidly implemented for disease research and drug toxicity screening, offering new opportunities for therapeutic intervention. However, obtaining cells in sufficient quantities with consistent quality at high purity is one of the hurdles that need to be addressed in order to broaden the applicability of these models. We anticipate that robust protocols will be developed in the next few years that reproducibly yield human iPSC-CMs with more adult phenotype, making them more amenable to large-scale production [19]. In addition, further refinement of differentiation protocols could lead to the generation of ESC- or iPSC-derived cardiac subtypes such as atrial, nodal, or ventricular cells [23].

Furthermore, the recent emergence of genome editing technologies in combination with iPSC technology could make it feasible to rapidly interrogate the effects of genetic modification in isogenic human model systems [24]. Genome editing by engineered nucleases is a promising approach that could be readily applied to patient-specific iPSC lines to correct or induce mutation-specific phenotypes in iPSC models. The ideal study design will probably involve the insertion of an inherited cardiomyopathy-related mutation into wild-type iPSC lines from diverse genetic backgrounds, which will allow investigators to test for causal effects of different mutations without the need for patient recruitment (Figure 2). In the long run, the creation of engineered human iPSC disease-in-a-dish models will enhance our understanding of underlying mechanisms related to inherited cardiomyopathies and provide a novel platform for patient-specific therapeutics.

Conclusion

The literature published in recent years demonstrates the growing importance of patient-specific iPSCs in disease modeling of inherited cardiomyopathies (Table 1). The identification of mutations in patients with inherited cardiomyopathies has revealed substantial molecular complexity in the etiologies of these disorders. Despite their complexity, the recent advancement of iPSC-based disease modeling *in vitro* has provided a human-based platform to improve our understanding of familial cardiomyopathies diseases. Follow-up research is expected to yield additional insights that will lead to new medical approaches to their treatment, but considerable work remains to be done.

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Key points

- HCM, DCM and ARVC/D have been recently modeled by patient-specific iPSC-CMs
- iPSC-CMs provide a novel human model to study the underlying molecular mechanism of the pathogenesis of inherited cardiomyopathies
- iPSC-CMs offer a human-based platform for *in vitro* drug screening and drug discovery

Figure 1. The genetic basis of inherited cardiomyopathies

Mutations in more than 50 genes have been associated with inherited cardiomyopathies, characterized by significant overlap. HCM, hypertrophic cardiomyopathy; DCM, dilated cardiomyopathy; LVNC, left ventricular non-compaction cardiomyopathy; ARVC/D, arrhythmogenic right ventricular cardiomyopathy/dysplasia.

Figure 2. Studying disease-causing gene variants by combining nuclease-mediated gene engineering and iPSC technologies

The genetic variability among human iPSCs can influence the outcome in cardiomyopathy modeling experiments. Nuclease-mediated gene targeting could in principle eliminate the variation arising from the iPSC line derivation and the genetic background. Isogenic iPSC lines carrying specific mutations can be generated using well-characterized parental iPSC lines derived from healthy patients of diverse genetic backgrounds. Generation of isogenic iPSC-CMs can be used to establish whether the observed phenotype is the direct result of the disease-causing variant independently of the genetic background noise. Functional assays can be performed to identify disease-related mechanisms. Similarly, this approach can be utilized in compound screening assays in order to determine the susceptibility of the genetic variant in question to drug-induced cardiac toxicity and arrhythmias. iPSCs, induced pluripotent stem cells; iPSC-CMs, induced pluripotent stem cell-derived cardiomyocytes.

Table 1

Recent publications on iPSC disease models of inherited cardiomyopathies

Disease	Gene mutation	Proband's phenotype	iPSC-CM phenotype	Drug testing	Ref
DCM	<i>TNNI2</i> p. R173W	Ventricular dilatation, systolic dysfunction	Altered Ca^{2+} regulation, reduced contractility, myofibril disarray	Metoprolol, SERCA2a overexpression, norepinephrine, Cisapride, Nicorandil, Alfuzosin, Verapamil	[10, 20]
	<i>DES</i> p. A285V	Ventricular dilatation, impaired left ventricular ejection fraction (LVEF), ventricular tachycardia	Diffuse abnormal DES aggregations	N/A	[11]
	<i>LMNA</i> p. R225X	Dilated right and left ventricles, impaired LVEF, atrial fibrillation, atrioventricular block	Nuclear senescence and cellular apoptosis	MEK1/2 inhibitors	[12]
HCM	<i>MYH7</i> p. R663H	Concentric left ventricular hypertrophy (LVH) with prominent thickening of the inferior septum and inferior wall	Cellular hypertrophy, disorganization of sarcomeres, calcineurin activation, nuclear translocation of NFAT, contractile arrhythmia and DADs, Ca^{2+} cycling dysfunction	Quinidine, Procainamide, Lidocaine, Mexiletine, Ranolazine, Flecainide, Propafenone, Propranolol, Metoprolol, Amiodarone, Sotalol, Dofetilide, Verapamil, Diltiazem, Nifedipine, Cisapride, Nicorandil, Alfuzosin	[6, 20]
ARVC/D	<i>PKP2</i> c.2484C>T c.2013delC	Severe right ventricular (RV) dilatation and reduced RV ejection fraction with no left ventricular impairment	Abnormal plakoglobin nuclear translocation and decreased β -catenin activity, exaggerated lipogenesis and apoptosis upon adipogenic stimulus, Ca^{2+} handling deficits	Overexpression of WT <i>PKP2</i> , PPAR- γ antagonists	[14]
	<i>PKP2</i> c.1841T>C	Dilated right ventricle with regional akinesia and reduced ejection fraction, normal left ventricular size and function	Decrease expression of <i>PKP2</i> protein, increased lipid accumulation upon adipogenic stimulus	N/A	[15]
	<i>PKP2</i> c.972InsT/N c.148_151delACAG/N	Dilated and trabeculated RV with reduced global RV function, ventricular tachycardia	Reduction in the gene expression levels of <i>PKP2</i> , desmosomal abnormalities, accumulation of lipid-droplets, upregulation of PPAR- γ	GSK-3 β inhibitor	[16]
LVNC	N/A	N/A	N/A	N/A	N/A
RCM	N/A	N/A	N/A	N/A	N/A