Induced Pluripotent Stem Cell-Derived Cardiomyocytes and Long QT Syndrome: Is Personalized Medicine Ready for Prime Time?

Silvia G. Priori

The study by Malan et al1 in this issue of the Circulation Research presents elegant data about induced pluripotent stem cell (iPSC)-derived myocytes2 from a mouse model of long QT syndrome (LQTS) type 3.3 The study is an important contribution that adds to a highly innovative field that is trying to define the role of iPSC technology in the understanding of inherited arrhythmias. In this accompanying editorial, I provide an overview of the previous studies in the field, comment on the contribution of Malan et al,1 and conclude by discussing some of the challenges in the field.

The Revolution Provided by iPSC Technology

The technique to differentiate cardiac myocytes from pluripotent stem cells is quite recent and it was introduced by the seminal article published in 2006 by Takahashi and Yamanaka,2 who used a combination of four retrovirally transduced transcription factors (Oct3/4, Sox2, Klf4, and c-Myc) to generate iPSCs from mouse somatic cells. The importance of this technology was immediately recognized and it was rapidly applied to human cells.4

In the past few years, several investigators have refined protocols to optimize differentiation of iPSCs into cardiac myocytes and to characterize their properties. In analogy with myocardial cells derived from human embryonic cells,5 iPSC-derived myocytes differentiate into three cell types: nodal, atrial, and ventricular myocytes and present physiological adaptation of action potential duration to changes in heart rate and normal response to beta adrenergic stimulation.6 Furthermore, the presence of key ion channels7 and regulators of intracellular calcium physiology,8 as well as the preservation of the sarcomeric structure,9 have been confirmed in iPSC-derived myocytes. This comprehensive set of data provided a solid background to test the hypothesis that the differentiation of iPSC-derived cardiac cells from patients with inherited cardiac diseases would allow the characterization of the behavior of mutant myocytes and even test their response to therapy.

iPSC-Derived Myocytes for Personalized Medicine

The proof of the concept that iPSC-derived myocytes from patients with inherited cardiac diseases presenting the phenotypic characteristics of the disease was published in 2010 by Carvajal-Vergara.10 The authors differentiated cardiomyocytes from patients affected by Leopard syndrome and carriers of the T468 mol/L mutation in the PTPN11 (protein tyrosine phosphatase, nonreceptor type 11) gene. Leopard syndrome patients presenting with cardiac hypertrophy and, in line with expectations, iPSC-derived cardiomyocytes derived from their fibroblasts showed increased surface area and a higher degree of sarcomeric organization as compared to myocytes derived from iPSCs of nonaffected individuals. Soon after the publication of the report by Carvajal-Vergara, the attention of investigators turned to the study of iPSC-derived myocytes from patients affected by LQTS.11–13 Such a strong interest toward LQTS is justified by the major advancements in the understanding of the genetic basis of LQTS14 that occurred in the past 15 years making genetic testing relevant for clinical management of LQTS patients.15,16

Despite that genotyping is actively pursued in LQTS patients, several challenges are still present in the interpretation of results of genetic testing, especially when novel mutations are identified and there is not adequate information to define their pathogenic role. In vitro characterization of mutations identified in LQTS genes that encode cardiac ion channels is regarded as a simple and reliable approach to define whether new mutations alter key properties of the ionic currents or impair protein assembly or localization. In addition, computer simulation studies using “in silico” models of action potential are used to investigate whether a mutation modifies the characteristics of the cardiac action potential.17 Despite that this approach is valuable and is currently accepted to define whether a genomic mutation is likely to be pathogenetic,18 it is clear that the availability of derived myocytes of the patient could provide a quantum leap in the bedside characterization of LQTS-related mutations.

iPSC-Derived Myocytes to Model Inherited Arrhythmogenic Diseases

Moretti et al in 201011 were the first to study iPSC-derived myocytes obtained from a LQTS patient carrier of the R190Q missense mutation in the KCNQ1 gene encoding for the alpha subunit of the channel that conducts the IKs repolarizing current. The KCNQ1(r190q) iPSC-derived cardiac myocytes showed a prolonged action potential and an impairment of

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trafficking and localization of the mutant channel to the surface of the cell. Interestingly expression of the KCNQ1R190Q mutation in COS cells had already predicted the inability of the mutant protein to properly coassemble and localize to the cell surface.

Soon after the report by Moretti et al, Yazawa et al characterized iPSC-derived myocytes from patients with type 8 LQTS carrier of the R406W mutation in the \( \text{CACNA1c} \) gene encoding for the alpha subunit of the voltage-dependent calcium channel. Biophysical properties of the Cav1.2R406W channel recorded from iPSC-derived myocytes were superimposable to those obtained by heterologous expression and showed a delayed inactivation of \( \text{ICa}^{\text{L}} \). Interestingly, however, Yazawa et al documented for the first time to our knowledge that the R406W mutation also leads to abnormalities of intracellular calcium physiology, an aspect that could not emerge through the study of the mutation in heterologous systems.

The characterization of iPSC-derived myocytes obtained from patients with LQTS type 2, ie, the genetic form associated with mutations on the \( \text{KCNH2} \) gene that encodes for the channel that conducts the IKr repolarizing current, was reported by Itzhaki et al. This study demonstrated that iPSC-derived cardiac cells with KCNH2A614V show prolongation of repolarization and are predisposed to develop early after depolarization.

In the context of these previous investigations, the study by Malan et al has successfully provided characterization of iPSC-derived myocytes from a knock-in mouse model with an in-frame deletion of three amino acids (del1505-1507) in the \( \text{SCN5A} \) gene that encodes for the alpha subunit of the Nav1.5 sodium channel. Malan et al therefore have provided the first iPSC-derived cardiac cell model of LQTS type 3. Studying \( \text{SCN5A}^{\text{del1505-1507}} \) iPSC-derived myocytes, these authors confirmed the biophysical results obtained in a heterologous system that showed a delayed inactivation of \( \text{INa} \) with sustained late sodium current. The important and original contribution of this study is the demonstration that, in response to rapid pacing, the action potential duration is able to shorten. This is a typical behavior of LQTS type 3 patients and confirms that iPSC-derived myocytes can recapitulate this distinguishing clinical feature of LQTS type 3.

**Prediction of Response to Drugs**

Yazawa et al and Itzhaki et al investigated the response to pharmacological interventions of the iPSC-derived myocytes from their LQTS type 8 and LQTS type 2 patients. Yazawa et al showed that roscovitine, a compound that increases the voltage-dependent inactivation of Cav 1.2 channel, restored the electric and \( \text{Ca}^{2+} \) signaling properties of Timothy syndrome cardiomyocytes by reverting the delayed inactivation of Cav1.2 associated with the G406R mutation. Similarly, Itzhaki et al tested different drugs in iPSC-derived KCNH2A614V cardiomyocytes. Exposure of KCNH2A614V iPSC-derived myocytes to the calcium channel blocker nifedipine or to pinacidil, a K\(_{\text{ATP}}\)-channels opener, produced a significant shortening of action potential duration, abolished early depolarization and triggered beats. Exposure of the KCNH2A614V cells to ranolazine, however, failed to shorten action potential duration, but it abolished early after depolarization and triggered beats. Based on these results, the authors propose that iPSC-derived myocytes might be used to predict response to drugs in patients. Such a conclusion seems to be premature considering that there is no clinical evidence that supports the prediction that nifedipine, pinacidil, or ranolazine may be effective in LQTS type 2.

**Balancing Challenges and Expectations**

Despite the exciting advancements made in the field of iPSC-derived myocytes to model LQTS, several challenges remain before a clinical use of iPSC-derived cardiomyocytes can be envisioned. The data collected up to now and discussed herein demonstrate that iPSC-derived myocytes obtained from LQTS patients recapitulate the key features of the disease, such as prolongation of action potential, development of early depolarization, and triggering of beats. Is this enough to legitimize the use of iPSC-derived myocytes in the clinical setting to devise personalized therapeutic approaches? I am convinced that the transition from “bench to bedside” will still require some time and a lot of work. Important limitations, such as the heterogeneity of the myocytes that are differentiated from LQTS iPSC-derived myocytes, question the clinical relevance of the information provided. As shown by Moretti et al, the differentiated cardiomyocytes are not identical cells, rather they comprise a continuum spectrum of different cells spanning from nodal to atrial to ventricular cells. This heterogeneity limits the ability to define the degree of prolongation of repolarization conferred by a mutation or the propensity of developing early depolarization with the accuracy required in the clinical arena. Furthermore, as highlighted by Malan et al, the stage of development is also an important factor that may influence the properties of iPSC-derived cardiac cells. Finally, arrhythmogenesis in the heart is influenced by factors that cannot be recapitulated by studying a single cell; therefore, the ability of iPSC-derived myocytes to predict response to therapy will require extensive investigations.

Time will tell if the iPSC technology can impact clinical management of LQTS. At present time, however, it seems that much more data are needed before iPSC-derived cells may become a paradigm for personalized treatment of LQTS patients.

**Disclosures**

None.

**References**


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