

Induced Pluripotent Stem Cell-derived Cardiomyocytes can Serve as Acellular Models for Cardiac Toxicity Testing

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Abstract

Induced pluripotent stem cell (iPSC) science is developing thrilling new possibilities for cardiovascular lookup by way of offering structures to learn about the mechanisms of ailment pathogenesis that ought to lead to new treatments or divulge drug sensitivities. In this review, the practicable usefulness of iPSC-derived cardiomyocytes in drug improvement as nicely as in drug toxicity checking out is discussed, with a center of attention on the achievements that have been already made in this regard. Moreover, the critical steps that have to be taken earlier than this science can be widely used in drug discovery and toxicology assessments are highlighted.

Keywords: Induced pluripotent stem cell; Drug toxicity; Drug development

Introduction

The discovery that somatic cells can be reprogrammed to pluripotent stem cells (induced pluripotent stem cells, iPSC), successful of differentiating to all cell types existing in the grownup organism, and specifically the fast adaptation of the science to human cells has generated giant expectations regarding the feasible applications. The science has an especially sturdy attraction for disciplines such as cardiovascular medicine, which deal with cell types (e.g., cardiomyocytes) that can't be effortlessly acquired from human probands or patients. Among the viable functions of iPSC technological know-how in the cardiovascular field, the workable usefulness in drug improvement as properly as in drug toxicity trying out has been already highlighted in the initial reviews on the technology of human iPSC. The goal of this evaluation is to outline the feasible position of iPSC-derived cardiomyocytes in this context, to factor out the achievements that have been already made in this regard, and to talk about the vital steps that have to be taken earlier than this technological know-how can be widely used in drug improvement and toxicity testing [1].

Possible Applications of Induced Pluripotent Stem Cell-Derived Cardiomyocytes in Drug Development and Toxicity Testing

The identification and characterization of possible drug targets, the screening of compound libraries for pills with a favoured effect, as properly as the assessment of drug candidates for viable detrimental results all require dependable check systems [2]. Such take a look at structures can be engineered primarily based on predominant cells, immortalized cell lines, or animal models; however, cardiovascular pharmacology suffers from numerous drawbacks of the currently-used take a look at structures primarily based on cardiomyocytes.

Primary human cardiomyocytes are now not effortlessly got and can't be stored in subculture for extended time intervals or multiplied in vitro [3]. Immortalized human cardiomyocyte telephone strains that faithfully mannequin necessary elements of cardiac physiology such as motion potentials are now not available. Alternatively, human phone cultures derived from embryonic sources, such as human embryonic kidney (HEK) lines, can be used to generate overexpression structures of the attainable drug goal molecule. This approves analyzing the outcomes of a drug on a precise gene or molecular mechanism, however fails to supply records on the compound's usual

cell (cardiomyocyte) outcome. Thus, currently, a lot of the lookup in this subject relies upon on animal models. For example, genetically-modified mice are regularly used to find out about the physiology that underlies human coronary heart disease. However, species variations are a applicable hassle if cardiomyocytes from laboratory animals are used to mannequin elements of human cardiovascular disorders [4].

Maturity of induced Pluripotent Stem Cell-derived Cardiomyocytes

A key hassle so some distance unresolved is posed by means of the truth that cardiomyocytes generated from pluripotent stem cells with the presently handy protocols are immature in contrast to their grownup counterparts. In many aspects, the cells are greater comparable to fetal than to grownup cardiomyocytes. Morphologically, the cells lack a fully-developed transverse tubule system. Functionally, the cells are regularly characterised through spontaneous contractions, which are no longer discovered in grownup ventricular cardiomyocytes [5]. The most diastolic membrane viable is much less terrible than that in grownup cardiomyocytes, and the motion plausible upstroke velocities and amplitudes are comparable to these of the 10-week-old embryonic hearts. Conflicting records exist concerning the maturity of the calcium managing gadget in pluripotent stem cell-derived cardiomyocytes, even though there is proof that at least simple aspects of the calcium biking equipment and excitation-contraction coupling are functional. The transcriptional profiles of iPSC-derived cardiomyocytes are additionally comparable to these of fetal cardiomyocytes [6].

Heterogeneity of Induced Pluripotent Stem Cell-derived Cardiomyocytes

The cardiomyocytes generated via contemporary differentiation

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Received: 23-Jul-22, Manuscript No. wjpt-22-70094; **Editor assigned:** 25-Jul-22, PreQC No. wjpt-22-70094 (PQ); **Reviewed:** 08-Aug-22, QC No. wjpt-22-70094; **Revised:** 16-Aug-22, Manuscript No. wjpt-22-70094 (R); **Published:** 23-Aug-22, DOI: 10.4172/wjpt.1000160

Citation: Yuan M (2022) Induced Pluripotent Stem Cell-derived Cardiomyocytes can Serve as Acellular Models for Cardiac Toxicity Testing. World J Pharmacol Toxicol 5: 160.

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protocols are a combination of cells belonging to all three primary cardiomyocyte subtypes: cells with atrial-, ventricular- and nodal-like phenotypes. While this can be regarded an benefit due to the opportunity to check physiological homes in all these telephone types, it additionally holds the downside that modifications that manifest solely in one subpopulation of cells can also be diluted if the readout is taken from all cells. Particularly, this trouble is possibly to occur in assays that do now not document the motion attainable of single cells, which is the most simple approach to classify every cell as atrial-, ventricular- or nodal-like. It is as a result necessary to recognize the mechanisms of cardiac subtype specification, and enormous efforts have been made to enhance protocols that minimize heterogeneity of human pluripotent stem cell-derived cardiomyocytes [7]. For example, inhibition of NRG-1b/ERBB signaling has been proven to beautify the share of nodal-like cells, and retinoid indicators beautify atrial versus ventricular specification for the duration of cardiac hESC differentiation.

Pharmacology of Induced Pluripotent Stem Cell-derived Cardiomyocytes- lessons from Disease Modeling Studies

Soon after the preliminary description of human iPSC, the first researches aimed at modeling cardiac ailments with patient-specific stem cells have been published. The first ailments that have been investigated the usage of this strategy had been monogenic channelopathies, such as extraordinary subtypes of long-QT syndrome or catecholaminergic polymorphic ventricular tachycardia (CPVT) [8]. The cell-autonomous pathophysiology of these problems approves the investigation of disease-specific phenotypes in single cells. Accordingly, single-cell methodologies such as patch clamp electrophysiology, fluorometric calcium imaging the usage of calcium-sensitive dyes and single telephone RT-PCR had been used in these studies. Most of these researches have already investigated the impact of pills on the patient-specific iPSC-derived cardiomyocytes. Drugs already acknowledged to have an impact on the disorder phenotype in sufferers (e.g., beta blockers in long-QT syndrome) had been used, on the whole to show that the in vitro disorder fashions recapitulate key aspects of the disease [9]. However, in some studies, novel pharmacological principles have been evaluated. For example, it used to be proven that dantrolene, a drug clinically used for the therapy of malignant hyperthermia, used to be capable to revert the arrhythmogenic phenotype in cardiomyocytes affected by way of CPVT precipitated by way of a mutation of the cardiac ryanodine receptor calcium channel.

Exploiting the Potential of Induced Pluripotent Stem Cell-derived Cardiomyocytes for Pharmacological and Toxicological Screening- Phenotype-Based Assays

In distinction to different structures often used in drug development, such as cell traces overexpressing precise ion channels, iPSC-derived cardiomyocytes undergo the practicable to be used in phenotype-based assays. In such assays, the readout is now not drug impact on a recognized goal shape (e.g., the modern mediated by means of a unique ion channel), however as a substitute a complicated phenotype, such as the beating rate, motion achievable duration, or the incidence of arrhythmias. A necessary benefit of such phenotypic assays is that it is viable to consider the impact of capsules that do no longer engage with recognized goal molecules. For example, the cardiac motion attainable is formed through the complicated gating conduct of greater than a handful of ion channels, many of which are composed of quite a few subunits encoded by means of unique genes. While the outcomes of a compound on a single ion channel gating can be studied in immortalized phone lines, such assays may additionally no longer

usually reply the query which impact the compound will have on a cardiomyocyte [10]. Many tablets that lengthen the QT interval do so by using inhibiting hERG activity, which can be assessed the use of hERG-overexpressing cell lines; different capsules (e.g., alfuzosin) do so by using a distinctive mechanism of action. The QT-prolonging (and consequently hazardous) viable of these capsules is consequently possibly to be neglected if relying completely on a hERG assay. On the different hand, there are drugs, such as verapamil, that block hERG in doses close to therapeutic plasma concentrations, however do no longer extend the QT interval in patients. Thus, similarly-behaving novel compounds may no longer enter the hospital currently due to being sorted out early in the drug improvement system due to their motion on hERG [11].

Assays that measure the motion attainable length in iPSC-derived cardiomyocytes may furnish a answer to these two problems. This has been validated with the aid of measuring motion plausible intervals in the total telephone patch clamp configuration in iPSC-derived cardiomyocytes: Alfuzosin, however now not verapamil drastically extended motion viable period in therapeutic concentrations, in distinction to the consequences on hERG elicited via the two drugs [12]. These observations may want to be additionally reproduced in an assay that used microelectrode arrays (MEA) to measure the area attainable duration, which is carefully correlated to the motion viable length of single cardiomyocytes. The use of MEA alternatively of single-cell patch clamp measurements is a necessary step toward growing the throughput of such assays.

To deliver the attainable of iPSC-derived cardiomyocytes for pharmacological and toxicological screening to fruition, the incorporation of these cells into dependable assays that can be scaled up to medium- or high-throughput functions would be desirable [13]. Several tries to attain this purpose have been already made. Drug-induced cardiotoxicity can show up as cardiomyocyte cell death. Using high-content computerized microscopy in a 96-well structure in conjunction with stay cell staining as properly as immunofluorescence, the impact of tablets on a panel of phone death-related abnormalities, such as nuclear structure exchange and fragmentation, DNA degradation, caspase activation, mitochondrial outer membrane permeabilization, and phone detachment was once assessed in iPSC-derived cardiomyocytes.

It is broadly identified that iPSC-derived cardiomyocytes have a massive attainable to strengthen drug improvement and toxicity testing. However, in order to fulfill this potential, quite a few necessary problems will have to be resolved. Standardization of techniques for iPSC generation, cardiac differentiation and nice manage will be imperative if these cells are to be included into standardized assays [14]. The business availability of well-characterized iPSC-derived cardiomyocyte may symbolize one essential step closer to this goal. The development of differentiation protocols in order to generate cells that are greater comparable to grownup cardiomyocytes is every other vital step. Depending on the deliberate application, the immature phenotype of cardiomyocytes generated with present day protocols may signify a extra or much less applicable problem. The most vital query that has to be answered for every proposed assay is to which extent the phenotype determined in iPSC-derived cardiomyocytes dealt with with a particular drug correlates with the scientific findings in sufferers handled with the identical drug [15]. This will have to be systematically investigated-with the aid of trying out as many pills as feasible as- earlier than the usefulness of the assay can be reliably predicted.

Discussion

Cardiotoxicity is a side effect associated with many drugs used to treat both cardiovascular and non-cardiovascular diseases. Screening for cardiotoxicity, especially prolongation of the QT interval, has eliminated many drugs early in the development pipeline, most appropriately, but the false positive and false negative rates are still unacceptably high. The development of a human cardiomyocyte-based platform for drug screening is being actively pursued in many arenas, and would represent a major advance in drug safety and efficacy testing.

Conclusion

Advances in pharmacogenomics have shown that an individual patient's gene polymorphisms can contribute to their susceptibility to the cardiotoxic effects of many drugs. GWAS studies are commonly used to identify these gene variants, however, once identified these gene variants must be confirmed and mechanisms for their effect defined. hiPSC-CMs represent a platform which has great potential for increasing the accuracy of these assessments, as drug responses in human cells are the best predictor of drug responses in the human heart. The generation of large biobanks of patient-derived hiPSC-CMs, representing patients with different genomic backgrounds, as well as from different racial and ethnic backgrounds, will allow us to more accurately identify drug efficacy and toxicity at the earliest stages of drug development.

Acknowledgement

I would like to acknowledge National Laboratory of Biomacromolecules, Institute of Biophysics, Chinese Academy of Sciences, Chaoyang, Beijing, China for providing an opportunity to do research.

Conflict of Interest

The authors declare that they have no conflicts of interest.

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