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Potential Role of iPSC Technology in Creating Exciting New Opportunities for Cardiovascular Research

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Abstract

By providing structures to learn about the mechanisms of disease pathogenesis that should result in new therapies or reveal medication sensitivities, induced pluripotent stem cell (iPSC) technology is creating exciting new opportunities for cardiovascular research. The practical relevance of iPSC-derived cardiomyocytes in drug development and toxicity testing is explored in this study, with a focus on the advancements that have already been accomplished in this area. Additionally, it highlights the crucial steps that must be accomplished before this research may be widely applied in drug discovery and toxicological evaluations.

Keywords: Induced pluripotent stem cell; Apoptosis; Cardiomyocytes; Drug development; Cardiotoxicity; Pharmacogenomics

Introduction

Huge hopes about the practical applications have been raised by the finding that somatic cells may be reprogrammed to become pluripotent stem cells (induced pluripotent stem cells, or iPSCs), which successfully differentiate into all cell types present in the adult body. Disciplines like cardiovascular medicine, which deal with cell types (such cardiomyocytes) that are difficult to get from human probands or patients, are particularly drawn to the science. The practical utility in medication development as well as in drug toxicity testing has already been emphasised in the earliest evaluations on the technology of human iPSC as one of the potential uses of iPSC in the cardiovascular sector. This evaluation's objectives are to describe the potential role of iPSC-derived cardiomyocytes in this context, to highlight the advancements that have already been made in this area, and to discuss the critical steps that must be taken before this technology can be widely used in drug development and toxicity testing. The discovery of Adverse Drug Reactions (ADRs), which may prematurely stop the torturous path of bringing a new chemical entity (NCE) to market, is one of the primary obstacles during the incredibly expensive and long process of drug development. Finding cardiotoxicity as one of the main causes for stopping the process is a crucial task in medication development. Numerous medications have been linked to a variety of cardiovascular side effects, including contractile dysfunction and electrophysiological disturbances that can result in life-threatening arrhythmias and heart failure. These disturbances include delayed and early-afterdepolarizations and triggered arrhythmias. According to reports assessing drug development failures between 2011 and 2015, lack of safety was the second most frequent reason for failure, with 24-28% of medications being discovered to be dangerous in clinical trials [1,2]. Cardiotoxicity ADRs may be found during the protracted drug development process or, worse, after the medication has been put on the market (i.e., post-marketing). This might have disastrous clinical consequences for the patients and place a heavy financial load on the insurance and healthcare systems. This article is divided into two parts to discuss important topics related to the process of drug development, in vitro disease modelling, and drug toxicity screening. In the first section, we concentrate on the process of developing new drugs and go into great detail on ADRs, drug-induced cardiotoxicity, safety screening when developing new drugs, and several processes behind ADRs. The second part is focused on the use of human induced pluripotent stem cell-derived cardiomyocytes (iPSC-CMs) for disease modeling and drug discovery. This section specifically discusses the justification for utilising iPSC-CMs and how to mimic both hereditary and acquired cardiac disorders using iPSC-CMs.

Drug development

Preclinical safety and pharmacokinetics evaluations of potential medications are crucial in the drug development process to make sure the safety profile is met. Removing a candidate medicine as early as feasible in the development process is vital and extremely effective, especially in light of the expensive and time-consuming process of bringing New Chemical Entities (NCE) to market. The inability to better assess and predict product safety results in failures during clinical development and, occasionally, after marketing, according to the US Food and Drug Administration (Food and Drug Administration (2004) Challenge and opportunity on the critical path to new medical products) [3].

Interactions between genetic, non-genetic, and environmental variables can result in patient-specific (adverse) medication responses. Pharmacogenomics, which is the use of genomic and other omic information to individualise medication selection and use in order to prevent adverse drug reactions and to enhance treatment efficacy, is an important subject that examines the impact of genetic variants on drug responses.

For instance, genetic differences in the production and operation of enzymes that metabolise drugs might affect plasma drug concentrations and thus result in ADRs. Pharmacogenomics may change pharmacokinetic and pharmacodynamic qualities and is influenced by genetic and epigenetic differences. Together with ADRs, this might explain a patient's unique reaction to a certain medicine; among the genetic variants, single-nucleotide polymorphisms (SNPs)

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play a key role. SNPs are DNA sequence variations that happen when a single nucleotide, such as adenine (A), thymine (T), cytosine (C), or guanine (G), varies across individuals or paired chromosomes in a species. It is now clear that epigenetics also produces inter-individual changes in phenotype, which may be significant with regard to ADRs susceptibility, in addition to the inter-individual differences generated by polymorphisms. The study of mitotically heritable changes in gene expression that are not due to changes in the nucleic acid sequence is known as epigenetics. To put it another way, epigenetics outlines the processes that give cells the ability to react fast to environmental changes and establish a connection between genes and the environment [4-7].

Through a variety of physiological processes, including changes to ion channels, altered intracellular Ca2+ handling, and increased cardiomyocyte death, drugs can induce cardiotoxicity. Depressed contractile function and an increased likelihood of ventricular arrhythmias are the results of these alterations. Since it has been obvious for years that ADRs, and particularly cardiotoxicity, must be screened for during the drug development process, many methods have been created to do so. The CiPA protocol has adopted the use of iPSC-CMs in the screening procedure to more accurately and sensitively detect proarrhythmic medication effects. However, myopathic effects are also a component of cardiotoxicity and may have negative clinical outcomes. In order to identify individuals who are more likely to have cardiotoxicity brought on by anti-neoplastic medications, several iPSC-CM models have been created. Similar to this, several iPSC-CM models for particular hereditary and acquired cardiac disorders have been reported. Further research is required to evaluate these models in the context of various medicines in order to enhance the identification of people at risk for DIC. The many iPSC-CM models for cardiac disease help to better understand certain disease pathways and might perhaps discover prospective pharmacological intervention targets. Opening up a brand-new and fascinating research area is the use of iPSC-CM illness models for drug discovery, employing either well-known or recently produced medications.

Cardiomyocytes produced from induced pluripotent stem cells may be used in medication development and toxicity testing

Reliable check systems are needed for the discovery and characterization of potential drug targets, the screening of chemical libraries for drugs with a desired effect, as well as the evaluation of drug candidates for realistic adverse effects. Such test structures can be created using primary cells, immortalised cell lines, or animal models, however the currently employed test structures based on cardiomyocytes have many shortcomings that make them unsuitable for cardiovascular pharmacology.

Primary human cardiomyocytes are currently difficult to obtain and cannot be multiplied in vitro or kept in subculture for a lengthy period of time. There are no immortalised human cardiomyocyte telephone strains available right now that can accurately imitate important features of cardiac physiology, such as motion potentials. Alternatively, human cell cultures with embryonic ancestry, like as human embryonic kidney (HEK) lines, can be used to make overexpression constructs of the desired therapeutic chemical. This enables research into a drug's potential impact on a particular gene or molecular mechanism, but it leaves out data on the drug's usual cell (cardiomyocyte) effect. As a result, animal models are still used extensively in research on this topic. As an illustration, genetically altered mice are frequently employed to study the physiology underlying human coronary heart disease [8]. However, if cardiomyocytes from laboratory animals are employed to model aspects of human circulatory diseases, species variances are a real problem. Maturity of cardiomyocytes generated from induced pluripotent stem cells. The fact that cardiomyocytes produced from pluripotent stem cells using the currently available procedures are immature in comparison to their adult counterparts poses a significant problem that has not been fully overcome. The cells resemble foetal cardiomyocytes more closely than adult cardiomyocytes in several ways. The cells don't have a completely formed transverse tubule system morphologically. In terms of functionality, the cells are frequently distinguished by spontaneous contractions, which are no longer seen in adult ventricular cardiomyocytes. The motion feasible upstroke velocities and amplitudes are equivalent to those of the 10-week-old embryonic hearts, and the most diastolic membrane viable is significantly less bad than that in adult cardiomyocytes. Although there is evidence that at least basic components of the calcium biking apparatus and excitation-contraction coupling are functioning, there are conflicting reports about the maturity of the calcium management apparatus in pluripotent stem cell-derived cardiomyocytes. Additionally, the transcriptional patterns of iPSC-derived cardiomyocytes and foetal cardiomyocytes are similar [9].

Heterogeneity of cardiomyocytes produced from induced pluripotent stem cells:

The cardiomyocytes produced by modern differentiation techniques are a mixture of cells with the characteristics of atrial, ventricular, and nodal cells, the three major cardiomyocyte subtypes. While the ability to examine physiological properties in all of these telephone kinds might be seen as a plus, it also has the drawback because readings from all cells may dilute changes that only affect a small subgroup of cells. This issue is most likely to arise in assays that do not record the motion that individual cells can undergo, which is the most straightforward way to categorise each cell as atrial-, ventricular-, or nodal-like. The processes of cardiac subtype determination must thus be understood, and great efforts have been made to improve techniques that reduce the heterogeneity of cardiomyocytes produced from human pluripotent stem cells. For instance, it has been demonstrated that blocking NRG-1b/ERBB signalling improves the proportion of nodal-like cells, and that retinoid markers improve atrial vs. ventricular determination during cardiac hESC differentiation.

Apoptosis (programmed cell death), which reduces the quantity of functioning cardiomyocytes and leads to decreased contractile performance and heart failure, is a significant contributor to severe cardiotoxicity. While having the intended cytotoxic impact that is responsible for the anti-cancer effectiveness of several drug families, particularly chemotherapeutics, they can also cause apoptosis, necrosis, or both. Anthracyclines, such as doxorubicin, have been shown to cause cardiomyocyte loss by triggering apoptosis in cultured cardiomyocytes like iPSC-CMs and experimental animals like mice and rats [10]. Several groups showed that doxorubicin-induced apoptosis is mediated by the generation of reactive oxygen species. The Tyrosine Kinases Inhibitors are a different class of anti-cancer medications that significantly increase cardiotoxicity (TKIs). The TKIs crizotinib and nilotinib have been shown to have cardiotoxic effects and to promote superoxide production, which explains the cardiotoxicity of the medications.

Lessons learned from research on disease modelling in the pharmacology of cardiomyocytes produced from induced pluripotent stem cells

The first studies targeted at using patient-specific stem cells to

simulate cardiac diseases were published not long after the initial description of human iPSC. Monogenic channelopathies, such as rare subtypes of long-QT syndrome or catecholaminergic polymorphic ventricular tachycardia, were the first diseases to be studied using this approach (CPVT). The study of disease-specific phenotypes in single cells is permitted by the cell-autonomous pathophysiology of these issues. As a result, single-cell methods such patch clamp electrophysiology, single telephone RT-PCR, and fluorometric calcium imaging using calcium-sensitive dyes were employed in these research. The majority of these studies have already looked into how medications affect patient-specific, iPSC-derived cardiomyocytes. Overall, it was demonstrated that the in vitro disorder models accurately reproduce the main features of the illness by using medications that are previously known to affect the disorder phenotype in patients (for example, beta blockers in long-QT syndrome). However, few research have explored new pharmaceutical concepts. As an illustration, it has been demonstrated that the medication dantrolene, which is therapeutically used to treat malignant hyperthermia, may reverse the arrhythmogenic phenotype in cardiomyocytes afflicted by CPVT that is caused by a mutation of the cardiac ryanodine receptor calcium channel.

Utilizing cardiomyocytes produced from induced pluripotent stem cells for pharmacological and toxicological screening using phenotype-based methods. iPSC-derived cardiomyocytes have the potential to be employed in phenotype-based experiments, as opposed to other structures frequently used in drug discovery, such as cell lines overexpressing specific ion channels. In these tests, the readout is no longer the effect of the medication on a known target shape (such as the contemporary controlled by a particular ion channel), but rather a complex phenotype, such as the beating rate, motion attainable duration, or the prevalence of arrhythmias. Such phenotypic tests have the essential advantage of making it possible to assess the effects of capsules that no longer interact with known target molecules [11-13]. For instance, the complex gating behaviour of a number of ion channels, many of which are made up of several subunits encoded by different genes, contributes to the formation of the cardiac motion. While a chemical's effects on a single ion channel's gating may be examined in immortalised cell lines, such experiments may no longer consistently provide an answer to the question of what effects the molecule would have on a cardiomyocyte. By suppressing hERG activity, which can be measured using hERG-overexpressing cell lines, many pills that prolong the QT interval work; however, some pills (such as alfuzosin) work in a different way. If relying solely on a hERG test, the QT-prolonging (and hence dangerous) viable of these pills may thus be disregarded. On the other hand, other medications, like verapamil, inhibit hERG at amounts that are near to therapeutic plasma concentrations yet no longer cause patients' QT intervals to lengthen. In light of the fact that similar-behaving innovative compounds are presently picked out early in the medication improvement system based on their action on hERG, they may no longer enter the hospital.

Discussion

These two issues could be solved by tests that gauge the range of motion that iPSC-derived cardiomyocytes are capable of. Alfuzosin, but not verapamil, significantly prolonged motion viable period in therapeutic concentrations, in contrast to the effects on hERG elicited by the two drugs. This was verified by measuring motion plausible intervals in the total telephone patch clamp configuration in iPSC-derived cardiomyocytes. These findings could also be confirmed in an experiment that measures the area attainable duration using microelectrode arrays (MEA), which is closely associated to the motion viable length of individual cardiomyocytes. To increase the throughput of such experiments, MEA must be used as an alternative to single-cell patch clamp measurements. The inclusion of these cells into reliable assays that can be scaled up to medium- or high-throughput functions would be required in order to realise the potential of iPSC-derived cardiomyocytes for pharmacological and toxicological screening. This goal has already been pursued in several attempts. Cell death in cardiomyocytes may be a symptom of drug-induced cardiotoxicity. The effect of tablets on a panel of cell death-related abnormalities, including nuclear structure exchange and fragmentation, DNA degradation, caspase activation, mitochondrial outer membrane permeabilization, and cell detachment, was once assessed in iPSC-derived cardiomyocytes using high-content computerised microscopy in a 96-well structure along with stay cell staining as well as immunofluorescence [14,15].

Conclusion

It is well known that iPSC-derived cardiomyocytes have a significant potential to enhance medication development and toxicity testing. However, a number of essential issues must be overcome in order for this potential to be realised. If these cells are to be included in standardised experiments, standardisation of methodologies for iPSC production, cardiac differentiation, and good management will be essential. Well-characterized iPSC-derived cardiomyocyte commercial availability may represent an important step toward achieving this objective. Another crucial stage is the creation of differentiation methods to produce cells that are more similar to mature cardiomyocytes. The juvenile phenotype of cardiomyocytes produced using current techniques may indicate an additional or much less relevant issue, depending on the purposeful application. To what degree the phenotype identified in iPSC-derived cardiomyocytes treated with a certain treatment coincides with the scientific findings in patients treated with the same agent is the most important question that must be addressed for each proposed test. Before the utility of the test can be confidently anticipated, this will need to be rigorously explored with the help of trying out as many tablets as practical.

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Conflict of Interest

Author declares no conflict of interest

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