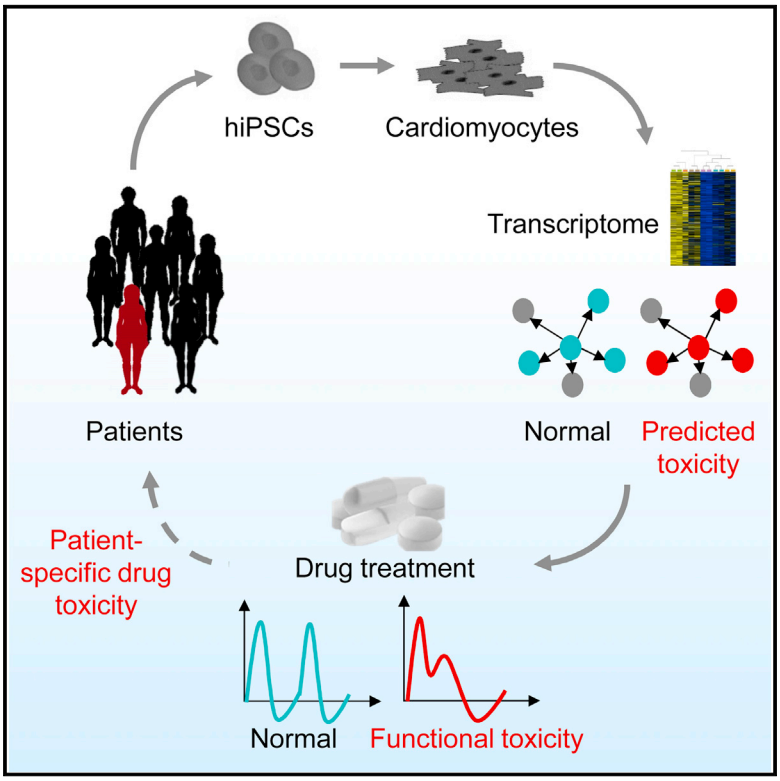
Article

Cell Stem Cell

Transcriptome Profiling of Patient-Specific Human iPSC-Cardiomyocytes Predicts Individual Drug Safety and Efficacy Responses In Vitro

Graphical Abstract



Highlights

- Reprogramming and cardiac differentiation preserve patient-specific gene expression
- Metabolic and stress genes account for inter-patient transcriptome variation
- Bioinformatics analysis predicts patient-specific drug-induced cardiotoxicity
- Drug-induced cardiotoxicity can be functionally evaluated in vitro using hiPSC-CMs

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In Brief

hiPSC-CM transcriptome profiling showed greater inter-patient than intra-patient variation. Toxicology analysis predicted and functionally validated individualized drug responsiveness, suggesting that hiPSC-CMs could serve as preclinical readout platforms for precision medicine.

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Transcriptome Profiling of Patient-Specific Human iPSC-Cardiomyocytes Predicts Individual Drug Safety and Efficacy Responses In Vitro

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SUMMARY

Understanding individual susceptibility to drug-induced cardiotoxicity is key to improving patient safety and preventing drug attrition. Human induced pluripotent stem cells (hiPSCs) enable the study of pharmacological and toxicological responses in patient-specific cardiomyocytes (CMs) and may serve as preclinical platforms for precision medicine. Transcriptome profiling in hiPSC-CMs from seven individuals lacking known cardiovascular disease-associated mutations and in three isogenic human heart tissue and hiPSC-CM pairs showed greater inter-patient variation than intra-patient variation, verifying that reprogramming and differentiation preserve patient-specific gene expression, particularly in metabolic and stress-response genes. Transcriptome-based toxicology analysis predicted and risk-stratified patient-specific susceptibility to cardiotoxicity, and functional assays in hiPSC-CMs using tacrolimus and rosiglitazone, drugs targeting pathways predicted to produce cardiotoxicity, validated inter-patient differential responses. CRISPR/Cas9-mediated pathway correction prevented drug-induced cardiotoxicity. Our data suggest that hiPSC-CMs can be used in vitro to predict and validate patient-specific drug safety and efficacy, potentially enabling future clinical approaches to precision medicine.

INTRODUCTION

Precision medicine is an emerging approach with great promise for disease prevention and treatment that takes into account individual variability in genes, environment, and lifestyle for each person (Collins and Varmus, 2015). It has rapidly become a major socioeconomic and health care focus, drawing attention to the need to develop appropriate research platforms to realize the promise of personalized patient care in the future. The advent of human induced pluripotent stem cell (hiPSC) reprogramming technologies (Takahashi et al., 2007; Yu et al., 2007) has not only circumvented ethical issues surrounding the use of human embryonic stem cells (hESCs) but also provided patient-specific cells that act as new platforms for the derivation of differentiated cell types that are ideal for disease modeling research, patient-oriented drug discovery, and toxicology studies (Matsa et al., 2014). In parallel, technological revolution in the "omics" field has enabled the cost-effective assembly of personalized and dynamic genetic information, providing unprecedented mechanistic insights into physiological states and disease susceptibility (Ozsolak and Milos, 2011). The combination of "omics" and hiPSC technologies provides unique opportunities for building preclinical functional readout systems that could serve as a solid foundation for precision medicine (Chen et al., 2016; Matsa et al., 2016).

Unpredicted drug-induced cytotoxicity has led to thousands of preventable hospitalizations and deaths. In addition, the resulting drug attrition has cost the pharmaceutical industry billions of dollars over the past decade (Laustriat et al., 2010). More than 30% of drugs entering clinical trials are withdrawn because of safety concerns, while the costs of drug discovery have climbed dramatically without a corresponding increase in the numbers of new drugs being released to the market (Scannell and Bosley, 2016). These problems point to the urgent need to develop more appropriate human in vitro models for preclinical patient-specific testing of drug candidates. Although the use of reprogramming technologies holds great promise for the generation of such models, in some studies, divergent reprogramming or differentiation strategies and chromosomal aberrations acquired during reprogramming and in vitro expansion, have