Report

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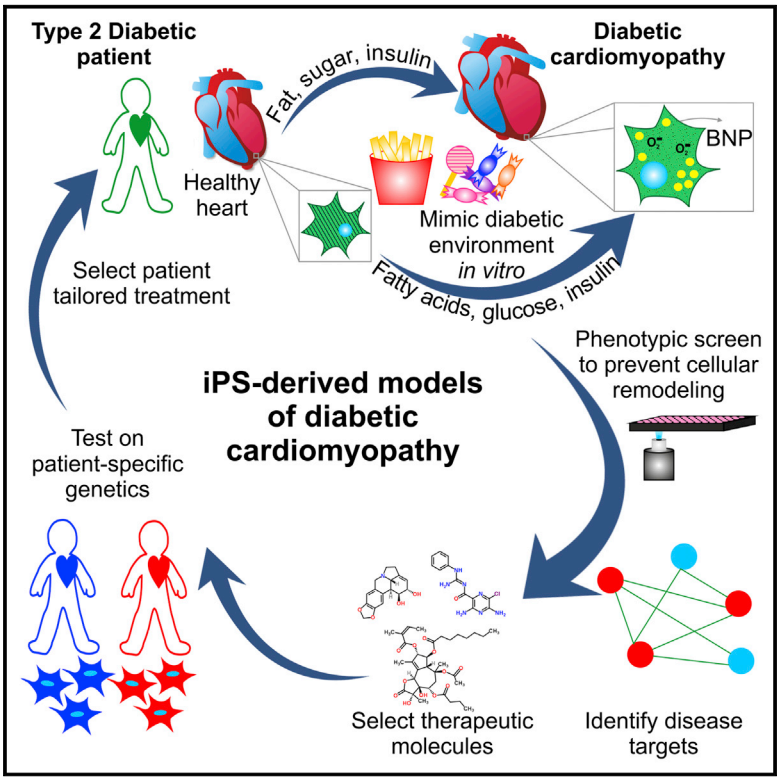
Disease Modeling and Phenotypic Drug Screening for Diabetic Cardiomyopathy using Human Induced Pluripotent Stem Cells

Graphical Abstract



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In Brief

Diabetes causes pathological remodeling of cardiac muscle, which impairs heart function. Drawnel et al. use induced-pluripotent-stem-cell-derived cardiomyocytes to develop environmental and patient-specific in vitro models recapitulating the condition. These models are harnessed in a phenotypic screening assay that identifies candidate protective molecules.

Highlights

Diabetic cardiomyopathy can be induced in vitro by environmental or genetic means

Diabetic patient-specific cardiomyocytes show baseline cardiomyopathy

The extent of patient-specific cardiomyopathy is clinically correlated

Phenotypic screening identifies drugs that rescue the disease phenotype

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Disease Modeling and Phenotypic Drug Screening for Diabetic Cardiomyopathy using Human Induced Pluripotent Stem Cells

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SUMMARY

Diabetic cardiomyopathy is a complication of type 2 diabetes, with known contributions of lifestyle and genetics. We develop environmentally and genetically driven in vitro models of the condition using human-induced-pluripotent-stem-cell-derived cardiomyocytes. First, we mimic diabetic clinical chemistry to induce a phenotypic surrogate of diabetic cardiomyopathy, observing structural and functional disarray. Next, we consider genetic effects by deriving cardiomyocytes from two diabetic patients with variable disease progression. The cardiomyopathic phenotype is recapitulated in the patient-specific cells basally, with a severity dependent on their original clinical status. These models are incorporated into successive levels of a screening platform, identifying drugs that preserve cardiomyocyte phenotype in vitro during diabetic stress. In this work, we present a patient-specific induced pluripotent stem cell (iPSC) model of a complex metabolic condition, showing the power of this technique for discovery and testing of therapeutic strategies for a disease with ever-increasing clinical significance.

INTRODUCTION

The World Health Organization estimates that the lethal clinical trajectory of type 2 diabetes mellitus (T2DM) will make it the seventh leading cause of death worldwide by 2030. Cardiovascular disease is the primary cause of death in this group, with data indicating that diabetes has a negative effect on cardiac muscle, independent of concurrent vascular influences such as coronary artery disease (Devereux et al., 2000). This condition is known as diabetic cardiomyopathy (DCM), which progresses to dilated cardiomyopathy and heart failure (Mandavia et al., 2013). T2DM induces specific cellular and molecular changes in the cardiomyocyte (CM), which lead to the pathology of these conditions. For example, the majority of the ATP required by healthy adult CMs is produced by fatty acid β-oxidation, with only a minor contribution from glucose and lactate oxidation. During nondiabetic cardiac disease and injury, CM metabolism reverts to an immature, fetal profile, with increased reliance on glucose oxidation (Lopaschuk and Jaswal, 2010). However, as a result of myocardial insulin resistance, T2DM promotes fatty acid β-oxidation in CMs, with pathological consequences (Heather and Clarke, 2011). First, fatty acid β-oxidation produces less ATP per O_2 consumed, reducing myocardial efficiency (Lorenzo et al., 2013). Second, toxic lipid metabolites such as ceramide accumulate in the CM, a response that is exacerbated by hyperlipidemia. Lastly, these metabolic changes distort CM structure. Mitochondrial dysfunction and reactive oxygen species (ROS) production activate ROS-sensitive proteases, which cleave myofilament proteins (Steinberg, 2013). Concurrently, oxidation-dependent ER stress impairs protein maturation and promotes degradation of newly synthesized proteins at the ER (Minamino and Kitakaze, 2010). Proteolytic damage and inadequate protein production synergize, resulting in loss of sarcomeric integrity. Together, these changes result in the clinical symptoms of DCM.

Despite its profound clinical impact, there is no specific treatment for DCM, and the complex etiology of the condition