iPSC modeling of heart disease for drug discovery

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Abstract:

Heart disease and failure remains the single largest source of mortality worldwide. However, compared to other indications, there are relatively few new drugs and therapeutic strategies. We have established an iPSC-based platform for discovery and validation of therapeutic targets using high throughput screens that scan the proteome and have applied it to explore therapeutic target space for inherited forms of Dilated Cardiomyopathy (DCM). DCM is a common cause for heart failure, and a third of cases have a genetic basis involving rare variants in about 50 genes. The heterogeneity of the disease-causing variants indicates diverse pathogenic mechanisms for inherited DCM. Unbiased screens of hiPSC-cardiomyocytes from DCM patients has uncovered candidate therapeutic targets that, when inhibited, are as potent at restoring contractile function as correction of the underlying genetic lesion. We have elucidated a few of the relevant mechanisms, including de novo serine/one-carbon metabolism and protein homeostasis, however a large number remain unexplored in the context of DCM or heart failure. In addition to discovery of novel therapeutic targets, we have used this platform to address the cardiovascular toxicity of an oncology drug, ponatinib. Ponatinib is a BCR-ABL kinase inhibitor used to treat chronic myeloid leukemia and has one of the highest incidences of adverse cardiovascular side effects. Phenotypic toxicity assays guided an SAR campaign that led to a refined analogue that appears to have a widened therapeutic window. We conclude that attention to cardiotoxic liabilities during early stages of oncology drug development might reduce their high incidence of cardiotoxicity, which can affect as many as a third of cancer patients. In summary, hiPSC technology has enabled the comprehensive mapping of therapeutic target space for DCM and have guided the medicinal chemistry optimization of a small molecule therapeutic to diminish its cardiotoxic liabilities.