Uncovering Molecular Mechanisms for Treatment of Congenital Heart Defects Through High-Content Genetic Perturbation Screens

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Congenital heart defects (CHDs) refer to structural defects in the heart that are present at birth. Hypoplastic Left Heart Syndrome (HLHS) is the most complex CHD and occurs when the left side of the heart is underdeveloped. It is responsible for 40% of neonatal cardiac deaths and, even with surgical interventions, reduces life expectancy by ~50 years. The underlying causes of HLHS are largely unknown, limiting development of targeted therapies. This study aims to uncover the molecular mechanisms of HLHS using genetic perturbations. Cardiomyocytes were differentiated from human induced pluripotent stem cells (hiPSCs) of both a patient affected by HLHS and his healthy father as a control. siRNA knockdowns systematically silenced 115 genes, with a distinct loss-of-function perturbation in each different cell. Immunostaining and high-content imaging quantified phenotypic changes, and a machine learning model was trained (86% accuracy) on control samples to classify perturbations as 'healthy' or 'unhealthy.' Additional analyses (Genome-Wide Association Studies, Principal Component Analysis, and feature correlation) identified key drivers of HLHS pathology. Genes that move patient cells toward a healthy-like state (PPP1R13B, RAI14, SIRT5) were identified as potential therapeutic targets with a 2.15-fold decrease in score ($p < 0.05$). Conversely, genes that drive father cells toward a patient-like phenotype (PBX1, NR6A1, PRDM16) were implicated in HLHS development with a 3.3-fold increase in score ($p < 0.05$). The acyl chain remodeling pathway was linked to these genetic changes, implying the role of lipid metabolism in disease development. These findings provide novel insights into HLHS pathogenesis and hold potential to improve diagnostic and therapeutic interventions.

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