A Novel In-Vitro Model of Pompe Disease using Human Induced Pluripotent Stem Cells

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Pompe disease (Glycogen storage disease type II) is an autosomal recessive disorder, caused by deficiency of lysosomal alpha-glucosidase (GAA), leading to progressive skeletal and cardiac muscle damage. Cardiac manifestations include hypertorhpic cardiomyopathy, heart failure and pre-excitation.

We report establishment of patient-specific *in-vitro* cardiomyocyte model of Pompe disease using human induced pluripotent stem cells (hiPSC). Dermal fibroblasts were obtained from a child with severe infantile pompe (frameshift mutation C341insT) and reprogrammed by retroviral delivery of Oct4, Sox2, and Klf2. Generated hiPSC were coaxed to differentiate into cardiomyocytes. Gene expression and immunostainings confirmed hiPSC pluripotency and cardiomyocyte phenotype.

Enzymatic activity (using a fluorescentic substrate) revealed lack of GAA activity in Pompe-hiPSC compared to healthy-controls. Electron microscopy showed excessive glycogen storage in pompe hiPSC-derived cardiomyocytes (hiPSC-CM) compared to healthy-control hiPSC-CM. Pompe hiPSC-CM showed enlarged glycogen-filled lysosomes between well-organized sarcomers as well as glycogen lakes, destroyed sarcomers, and abnormal mitochondria.

We tested the role of enzyme replacement in preventing and reversing glycogen storage. Treatment with 100mcg/ml of recombinant human GAA resulted in sustained GAA activity (comparable to normal cells) for at least 96 hours post-treatment. Treatment reduced glycogen storage, improved sarcomeric organization within 1 week and prevented glycogen storage in continuously treated cells. *Conclusions:* Our study demonstrates, for the first time, ability to model the abnormal phenotype of an inherited metabolic cardiomyopathy using the emerging hiPSC technology and represents a novel paradigm to study disease mechanisms and treatment. Specifically, in Pompe disease, it enables elucidation of mechanisms underlying glycogen storage and cardiac hypertrophy and screening of new treatment options.