Modeling the Long QT Syndrome with Induced Pluripotent Stem Cells

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The congenital long QT syndrome (LQTS) is a familial arrhythmogenic syndrome, characterized by abnormal ion channel function and sudden cardiac death. We hypothesize that the generation of patient-specific human induced pluripotent stem cells (hiPSCs) will allow the establishment of a novel in-vitro model of the LQTS; providing mechanistic information and aiding in screening of potential disease aggravators and therapeutic strategies.

Dermal fibroblasts, obtained from a LQTS-type-2 patient (characterized by the A614V missense mutation in the KCNH2 gene), were reprogrammed by retroviral delivery of Oct4, Sox-2, and Klf-4. The generated hiPSCs lines were coaxed to differentiate into the cardiac lineage. Detailed whole-cell patch-clamp and extracellular multielectrode recordings demonstrated significant prolongation of the action-potential duration in the LQTS-hiPSCs-derived cardiomyocytes (the characteristic phenotype of the LQTS) when compared to healthy-control hiPSCs-derived cardiomyocytes. Voltage-clamp recordings showed significant diminution of the IKr current in the LQTS-cardiomyocytes. The LQTS-derived cells also displayed marked arrhythmogenicity; characterized by the development of early after depolarizations (EADs) and triggered arrhythmias. We then utilized the LQTS-hiPSC-derived cardiac tissue model to evaluate the potency of existing and novel pharmacological agents that may either aggravate (potassium channel blockers) or ameliorate (calcium channel blockers, KATP channel openers and late-sodium channel blockers) the disease phenotype.

Our study illustrates the ability of the hiPSCs technology to model the abnormal functional phenotype of an inherited cardiogenic disorder and to identify potential new therapeutic agents. As such, it represents a promising paradigm to study disease mechanisms, optimize patient care (personalized medicine), and aid in the development of therapies that may find their way to the bedside.