Title: Modeling hypertrophic cardiomyopathy with human heart organoids

Authors:
Martta Häkli & Katriina Aalto-Setälä

Keywords:
human induced pluripotent stem cell; cardiomyocyte; human heart organoid; hypertrophic cardiomyopathy

Abstract
Hypertrophic cardiomyopathy (HCM) is the most common genetic cardiovascular disease caused by several known mutations, mostly in sarcomeric genes. However, it can also be caused by non-sacromeric genes, such as the less studied heterozygous Finnish founder mutation c.482C>A, p.(Thr161Lys) in junctophilin-2 (JPH2). The mutation carriers suffer from significant septal thickening and have a high prevalence of arrhythmias. JPH2 is a structural protein connecting cell membrane to sarcoendoplasmic reticulum and has a crucial role in efficient calcium handling and contraction of cardiomyocytes (CM).

This study aims to model HCM caused by the JPH2 mutation in human heart organoids (hHOs) to elucidate HCM disease phenotype, progression and mechanisms. Human heart organoids can be generated from induced pluripotent stem cells (hiPSCs), which will self-assemble into heart organoids and differentiate into several cardiac cell types, including CMs, cardiac fibroblasts (CF), endothelial cells (EC), epicardial cells (EPI) and vascular smooth muscle cells (VSMC). Especially CFs have a key role in development of fibrosis in HCM, which is one of the key features of the disease.

In this study, hiPSCs derived from healthy control and HCM patient carrying the JPH2 mutation, as well as a hiPSC line with isogenic correction of the mutation will be used to generate hHOs. The hHOs will be cultured for 2-6 weeks, and the disease progression and phenotype will be evaluated using video microscopy and calcium imaging to assess the contractility and arrhythmogenicity, as well as immunocytochemical staining and RT-qPCR to assess cellular composition of the hHOs, CM hypertrophy and fibrosis.