Fatty acid-stimulated maturation of hiPSC-derived cardiomyocytes in Engineered Heart Tissue

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Cardiac metabolism and function are linked as substrate metabolism generates the energy which enables the heart to beat. Human heart cells can be studied in vitro using human induced pluripotent stem cell-derived cardiomyocytes (iPS-CM). However, when cultured in normal media, iPS-CM use glucose as the primary substrate whereas adult cardiomyocytes generate energy predominantly through fatty acid oxidation (FAO). Culture in 3D in engineered heart tissue (EHT) induces iPS-CM to attain a more mature phenotype and upregulate FAO.

Here we aimed to further induce FAO, by addition of oleic acid (OA), to drive iPSC-CM to a metabolically flexible mature phenotype. Substrate metabolism in iPS-CM grown in monolayers and in EHT was characterised by measuring gene expression, the uptake of radiolabelled glucose and fatty acids, structural phenotyping, and mitochondrial activity. Addition of 400 mM oleic acid for one week decreased the rate of glycolysis in monolayer iPS-CM from 200 to 100 nmoles per 10^6 cells/hour and increased FAO from 0.3 to 0.5 nmoles per 10^6 cells/hour. FAO was 4-fold higher in EHT than in cells grown as a monolayer whilst the rate of glycolysis decreased to 25 nmoles per 10^6 cells/hour. Immunocytochemistry for α-actinin showed formation of striated mycoytes.In EHTs, addition of OA did not change the rate of glycolysis but OA treatment induced a further increase in FAO from 1 to 1.4 nmoles per 10^6 cells/hour. This switch was associated with changes in metabolic and structural gene expression towards a more mature phenotype.