

Objective The ability to derive cardiomyocytes from human induced pluripotent stem (iPS) cells provides a novel approach to study inherited cardiac channelopathies. Fibroblasts from patients can be reprogrammed to iPS cells and differentiated into cardiomyocytes that carry the patient's exact genetic background. Although this technique has enormous potential for modeling inherited channelopathies the derived cardiomyocytes have not been fully characterised and compared to adult and foetal cells. Knowledge about their maturity will be critical if assessments of cellular function are to provide insight into disease processes that manifest in the adult.

Methods Healthy control human iPS cells were differentiated into cardiomyocytes using an unguided differentiation protocol. Embryoid bodies from undifferentiated iPS cells were cultured in suspension for 4 days before being plated onto 0.1% gelatin. Spontaneously contracting areas were disaggregated and single cardiomyocytes were characterised using immunocytochemistry, TEM, electrophysiology and Ca^{2+} imaging. Cells were stained for Troponin T, Troponin I and α -actinin. Ca^{2+} release into the cytoplasm was detected by fluo-4 and fluorescence intensity was traced before and after Tetrodotoxin (TTX) treatment. Sodium channel activity was measured in a low sodium buffer using perforated patch-clamping. Ultrastructure of cells was analysed with transmission electron microscopy while the presence of t-tubules was investigated using the fluorescent dye Di-8-ANEPPS. Cardiac cells derived from iPS cells were then compared to primary cardiomyocytes isolated from human foetal and adult cardiac tissue.

Results iPS derived cardiomyocytes express a wide range of cardiac markers as well as Tetrodotoxin resistant voltage activated sodium channels that inactivate and recover from inactivation and exhibit action potential triggered Ca^{2+} -induced- Ca^{2+} -release. Spontaneous contraction and lack of t-tubules were observed in derived cardiomyocytes and immature human foetal cardiomyocytes.

Conclusion iPS cells give rise to mostly immature cardiomyocytes, that express typical cardiac proteins and have functional cardiac sodium channels. This differentiation system may be utilised to investigate patients with and without known genetic mutations to provide a better understanding of the pathophysiology of inherited cardiac channelopathies.