Mini-HEART - Human mini hearts: looking for culprits and victims in cardiac disease

Cardiac disease causes morbidity and mortality as frequently as cancer. Predicting cardiac arrhythmia and cardiac failure, understanding multicellular (patho)physiological mechanisms, and devising new treatments represent unmet needs in the field. Human induced pluripotent stem cells (hiPSC) could revolutionise the way we study human disease but unfortunately, they still fall short in recapitulating variable phenotypes and complex cardiovascular diseases. This is partly due to functional immaturity of hiPSC-derived cardiac tissues, shortage of methods for accurate functional analysis and inability to identify cell-type specific contributions to disease pathology. I will address these challenges in Mini-HEART. We recently assembled novel three-dimensional multi-cellular cardiac microtissues as an important step towards full maturation and used these to demonstrate that cardiac disease mutations might directly affect non-myocyte cardiac cells. However, application of hiPSC microtissues to precision medicine remains to emerge. Using a multidisciplinary approach, I will combine isogenic hiPSC, their differentiation into distinct cell types of the heart, multifaceted biophysical assays, and tissue engineering to prove cell-type causality of disease and identify new molecules targeting the culprit cells to rescue the disease phenotype. I plan to use our unique complex hiPSC-cardiac microtissue to 1) identify and synthetically enhance maturation mechanisms; 2) reveal late arrhythmic and fibrotic phenotypes; 3) dissect cell-type specific contributions to complex cardiac diseases, including the role of macrophages and sympathetic nerves; 4) test two therapeutic strategies based on drug-tailoring and gene editing, to modulate the disease phenotype. Together, Mini-HEART will create new opportunities for designing novel biomedical tools to i) capture phenotypic changes, ii) reveal (patho)physiological mechanisms and ii) develop new therapeutic approaches for heart disease.

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