EuroSciCon

2nd Edition of EuroSciCon Congress on

Heart Disease and Interventional Cardiology

February 25-26, 2019
Paris, France

Interv Cardiol J 2019, Volume: 5
DOI: 10.21767/2471-8157-C1-006

MANY CELLS MAKE LIFE WORK: MULTICELLULARITY IN STEM CELL-BASED CARDIAC DISEASE MODELLING

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Cardiac disease causes 33% of deaths worldwide but our knowledge of disease progression is still very limited. In vitro models utilizing and combining multiple, differentiated cell types have been used to recapitulate the range of myocardial microenvironments in an effort to delineate the mechanical, humoral and electrical interactions that modulate the cardiac contractile function in health and the pathogenesis of human disease. However, due to limitations in isolating these cell types and changes in their structure and function in vitro, the field is now focused on the development and use of stem cell-derived cell types, most notably, human-induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs), in modeling the cardiomyocyte function in health and patient-specific diseases. It is becoming increasingly appreciated that communications between cardiomyocytes, the contractile cell of the heart, and the non-myocyte components of the heart regulate cardiac development and maintenance of health and adult cardiomyocyte functions, including the contractile state. They also regulate remodeling in diseases, which may cause the chronic impairment of the contractile function of the myocardium, ultimately leading to heart failure. Within the myocardium, each cardiomyocytes is surrounded by an intricate network of cell types including endothelial cells, fibroblasts, vascular smooth muscle cells, sympathetic neurons and resident macrophages and the extracellular matrix, forming complex interactions and models utilizing hiPSC-derived cell types offer a great opportunity to investigate these interactions further. We outline the historical and current state of disease modeling, focusing on the major milestones in the development of stem cell-derived cell types and how this technology has contributed to our knowledge about the interactions between cardiomyocytes and key non-myocyte components of the heart in health and disease, in particular, heart failure. Understanding where we stand in the field will be critical for stem cell-based applications-including modeling diseases that have complex multicellular dysfunctions.

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