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Human stem cell-based *in vitro* model of cardiac hypertrophy

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i Biotech-huset, Arvid Wallgrens Backe 20, fredagen den 9 december, klockan 13.00

av Markus Johansson

Fakultetsopponent:
Professor Chris Denning
University of Nottingham, United Kingdom

Avhandlingen baseras på följande delarbeten

I. Johansson, M., Ulfenborg, B., Andersson, C.X., Heydarkhan-Hagvall, S., Jeppsson, A., Sartipy, P. and Synnergren, J. *Cardiac hypertrophy in a dish: a human stem cell based model*
Biology Open. 2020 Sep;9(9):bio052381

II. Johansson, M., Ulfenborg, B., Andersson, C.X, Heydarkhan-Hagvall, S., Jeppsson, A., Sartipy, P., and Synnergren J. *Multi-Omics Characterization of a Human Stem Cell-Based Model of Cardiac Hypertrophy*
Life. 2022 Feb;12(293):life12020293

III. Johansson, M., Tangruska, B., Heydarkhan-Hagvall, S., Jeppsson, A., Sartipy, P., and Synnergren, J. *Data Mining Identifies CCN2 and THBS1 as Biomarker Candidates for Cardiac Hypertrophy*
Life. 2022 May;12(726):life12050726

IV. Johansson, M., Heydarkhan-Hagvall, S., Jeppsson, A., Sartipy, P., and Synnergren J. *Characterization of the hypertrophy response in Endothelin-1 stimulated cardiomyocytes: A single cell study*
Manuscript

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Human stem cell-based *in vitro* model of cardiac hypertrophy

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Abstract

Cardiac hypertrophy is an important and independent risk factor for the development of cardiomyopathy that may lead to heart failure. To accelerate the development of new and improved treatment options, relevant disease models that can be used to understand the pathological drivers, and to screen new potential drug candidates are urgently needed. Today, many cardiovascular disease models are animal based, which may limit the translatability of the results and there are also strong ethical reasons to reduce the use of experimental animals.

The aim of this thesis was to develop a human stem cell based *in vitro* model of cardiac hypertrophy and thoroughly characterize the hypertrophy response in the cardiomyocytes during various conditions. We also sought to use the model for identification of possible candidate hypertrophy biomarkers. Finally, we studied the model on a single-cell level in an attempt to identify possible subgroups of cardiomyocytes and determine if they displayed a differential response to endothelin-1 (ET-1) stimulation.

The disease model was shown to recapitulate a characteristic cardiac hypertrophy response on functional, transcriptomic, and secretomic levels. The results showed that the cardiomyocytes responded, in a time-dependent manner, to the hypertrophic stimulation with ET-1 by an increase in cell volume, increased glucose consumption, and a significant change in gene expression profile indicative of a hypertrophic phenotype. Pathway enrichment analysis also showed that signaling pathways involved in cardiac hypertrophy were altered. Additionally, analysis of the secreted proteins during ET-1 stimulation identified several proteins with the potential to be further explored and developed to cardiac hypertrophy biomarkers for use in the clinic.

The single cell analysis did not reveal distinct subtypes of cardiomyocytes in the cultures. However, a group of cardiomyocytes that showed higher expression of fetal genes was observed, indicating a more immature type of cardiomyocytes. The response to ET-1 stimulation was relatively homogenous among the cells, with no distinct groups that responded differently.

In summary, the work in this thesis presents a disease model of cardiac hypertrophy that can be useful for various applications, including studying disease mechanisms and the identification of potential biomarkers. Moreover, the model can serve as a starting point when developing more advanced disease models that are cultured in, e.g., a 3D-organoid culture system.

Keywords: bioinformatics, cardiac hypertrophy, cardiomyocytes, disease model, human pluripotent stem cells, proteomics, secretomics, transcriptomics

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