Transcriptomic insights into cardiac healing - unveiling promising targets for effective gene therapies in diseased hearts

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Identifying therapeutical target genes is the first step towards developing new gene therapies to promote cardiac repair after injury. In the last decades, despite the many steps forward, not a single therapy has shown to be effective and suitable for human treatment of the injured heart. Considering that cardiac diseases represent one of the most prevalent causes of morbidity, disability, and mortality in the world, it is, therefore, essential to develop new and improved therapies to induce cardiac regeneration.

In this study, we aimed to identify novel therapeutical targets that could be used for future purposes of cardiac gene therapy. Unlike previous studies that investigated fetal hearts that are physiologically and functionally different from mature hearts, we focused on investigating adult human hearts that we collected from human donors with post-mortem time below 5 hours. Samples of left ventricles were molecularly and morphologically characterized for the presence of stress, cardiac damage, and cardiac fibrosis. Results of the molecular analyses were cross-referenced with the donors' medical history to classify each specimen as "control" or "diseased." Next, we performed single nuclei RNA sequencing of samples of the left ventricle from 2 "control" and 3 "diseased" hearts. Due to the adult tissue's complexity and the specimen's high-fiber content, we optimized the nuclei isolation protocol. Eventually, we successfully sequenced an average of 8,000 nuclei per sample with a gene coverage of approximately 800 genes per nucleus, identifying, via unsupervised cluster analysis, 17 different cell populations.

In cardiomyocytes, we identified over 500 genes differentially expressed in diseased hearts when compared to healthy controls. Among these genes, we discovered several novel target genes whose expression is increased only in diseased cardiomyocytes. Gene ontology analysis of the known interactors of the newly identified target genes shows enrichment in terms such as sarcomere organization, muscle contraction, mitochondrial energetics, calcium handling, and fatty acid metabolism.

Currently, we are investigating the molecular effects of the gain and loss of function of these genes in healthy iPS-derived cardiomyocytes and human-derived myocardial tissue slices to better understand their role in the pathophysiology of the adult human heart. From a therapeutic perspective, our ongoing research holds promises for developing new and improved intervention therapies to promote cardiac regeneration.

![Diagram](image-url)