Thesis title:

Molecular Changes In Heart During Post Myocardial Infarction Remodeling In A Murine Model

Abstract:
Cardiovascular diseases (CVDs) are the number one cause of mortality worldwide. Most types of CVDs result in heart failure and death as a common outcome. Of all the types of CVDs, myocardial infarction (MI) is the most prevalent which can result in heart failure through a process known as post MI remodeling. In this study we have utilized iTRAQ proteomic technique to find out the global proteome changes during post MI remodeling in order to discern the major cellular networks and proteins involved that direct the heart towards failure. We have considered the infarct and non-infarct regions of the heart during early and late time points of remodeling to get an exhaustive profile of the changes that occur, in this essentially time dependent process.

Proteomic analyses have revealed that various networks of cardiac metabolism are profoundly affected at all spatial regions and time points of study. Besides beta and glucose oxidation, ketone body and branched chain amino acid oxidation pathways showed alteration along with citric acid cycle and mitochondrial electron transport chain to result in drastic changes in myocardial ATP content. Unique alteration in the cytoskeletal proteins was found in this study during both MI and post MI time points.

Further studies were carried out with the cytoskeletal protein Desmin and the mitochondrial protein HSD17B10. Desmin was found to be partially cleaved by the neutral proteinase Calpain1, in the infarct zone, forming insoluble aggregates in the myocytes which may hamper the contractile function of these cells. HSD17B10 was found to be downregulated during late phase remodeling resulting in the accumulation of unprocessed mitochondrial tRNA species. It led to hampered mitochondrial protein translation, reduced activity of the mitochondrial complexes and energy dysfunction. Taken together, this study has provided a composite picture of the proteome alterations taking place during post MI remodeling and identified two unique mechanisms that may be responsible for the compromised cardiac function seen during the progression of this condition to heart failure, to serve as potential therapeutic targets, subject to future investigation.

Attested
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