Impact of Autophagy Regulating Extracellular Biomarkers in Cardiovascular Disease

Hypertrophic cardiomyopathy (HCM), a disease in which heart muscle cells (cardiomyocytes) enlarge leading to abnormal myocardial thickening, is a major contributor to heart failure and the most common cause of sudden cardiac death. It requires either a heart transplant or invasive surgical procedures to physically thin the heart muscle, both of which are dangerous and can lead to significantly reduced quality of life. While HCM is a genetically inherited disease, there is currently a lack of an early predictor of the disease before irreversible cardiac dysfunction and heart failure. Research has identified key proteins responsible for actin-cytoskeleton organizations such as MYBPC3 and FHOD3 as drivers of HCM. Recently, molecular crosstalk between autophagy machinery (an important cellular stress response mechanism) and extracellular exosomes has been implicated in HCM. Elucidating specific extracellular microRNAs has the potential to reveal early molecular markers of HCM, where interventions can be applied to help patients.

The overall hypothesis I will be seeking to test is whether circulating microRNAs that modulate the autophagy machinery are integral to maintaining cardiomyocyte health and volume. My project thus aims to profile the expression levels of microRNAs known to regulate autophagy in several models of HCM. This would allow me to identify a subset of microRNAs important for HCM that are up-regulated or down-regulated similarly in both mice and in humans. I plan to do a functional study on whether the microRNAs are sufficient to induce the HCM phenotype.

Specifically, I plan to induce hypertrophy in cultured murine cardiomyocytes with the Bioflex system to simulate biomechanical stress seen in HCM hearts. I will then perform chromatography to purify extracellular vesicles from three HCM models: a) growth media of cultured murine cardiomyocytes, b) plasma from HCM transgenic mice, and c) plasma from HCM human patients. To observe changes in microRNA expression in extracellular exosomes, I will isolate total microRNA and run qPCR with primers specific to autophagy-regulating microRNAs. By subsequently incubating the microRNAs with healthy cardiomyocytes, I will study the effect of autophagy proteins via Western Blot, on cell energetics via fluorescent mitochondrial probes, and on cell size using microscopy.

As a member of the Chen Lab since last semester, I have been learning cell and molecular biology laboratory techniques from Dr. Boukhalfa at the Molecular Cardiology Research Institute. By utilizing HCM primary cardiomyocyte samples from Tufts Medical Center, I plan to conduct my research project under the continued guidance of Dr. Boukhalfa. Furthermore, I will meet regularly with Dr. Chin and Dr. Huggins, cardiologists and HCM experts at Tufts Medical Center, as a committee to discuss my research progress. Combined with the fundamental knowledge gained from my academic experience, I look forward to further exploring the role of specific exosomal microRNAs in predicting the early stages of HCM and the molecular markers of the disease, ultimately allowing me to develop skills for cardiovascular disease research and medicine.