A Novel Systemic Approach to Cardiometabolic Disease with Dual Therapeutics

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Cardiometabolic disease (CMD) is a cluster of correlated diseases. Risk of heart disease, the world's leading cause of death, is greatly increased by metabolic syndrome, a combination of diabetes, hyperlipidemia, and hypertension. A rapidly growing global public health challenge, CMD affects 25% of global adults and 50% of US adults. Novel therapeutics must target disease commonalities of underlying pathways—oxidative stress, fatty acid oxidation, glucose metabolism—across multiple tissues. Thus, FOXO and AMPK proteins were investigated as a potential dual therapeutic, as they regulate key metabolic pathways in adipose tissue, the major lipid repository, and skeletal muscle, where 80% of glucose uptake occurs. FOXO and AMPK were expressed in adipose and muscle by creating 6 transgenic Drosophila crosses. CMD was induced with high fat/sucrose diets. Heart and thorax surgeries, beating heart video analysis, confocal imaging, and hemolymph extraction were performed to assess 7 key indicators: glucose levels, cardiac function and structure, lipid accumulation, skeletal muscle structure, flight ability, and survival rate. AMPK in muscle treated hyperglycemia, decreasing glucose by 82%($p<0.05$), enhanced flight ability, and mitigated skeletal muscle atrophy and disarray. FOXO in adipoctyes significantly reduced cardiac impairments(contractility improved 140%, arrhythmicity 90%, heartrate 50%,$p<0.05$), decreased lipid accumulation(reduced adipocyte size and count) and preserved myocardial structure(treated hypertrophy and fibrillar disarray). Both FOXO and AMPK doubled survival rates. This research sheds light on the cellular and molecular mechanisms by which FOXO and AMPK mitigate CMD. Furthermore, this study presents FOXO and AMPK as an effective combinatorial CMD drug target.

Awards Won:

Second Award of $2,000

American Statistical Association: Certificate of Honorable Mention