Importance of Per2 in Cardiac Mitochondrial Function during Stress

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Background/Objective: Ischemic heart disease is the worldwide leading cause of death. Cardiac cellular damage from ischemia is mainly inflicted in the form of mitochondrial dysfunction by inflammatory cytokines and reactive oxidative species (ROS). Mitochondria are critical for metabolic function to maintain cardiac activity. Interventions against inflammatory cytokines and ROS are therefore cardioprotective during ischemic damage. Period Circadian Regulator 2 (Per2) is a circadian rhythm protein involved in metabolic regulation as a time-responsive gene in cardiomyocytes during ischemic damage. Overexpression of Per2 has been shown to decrease infarct size following myocardial infarction. In this study, we hypothesize that Per2 protein plays a regulatory role in the mitochondrial response to inflammatory cytokine TNFα and oxidative stressor H2O2 in human cardiomyocytes.

Methods: AC16 Human Cardiomyocytes (HCM) transfected with Per2 or control siRNA were subjected to stress treatment of 100ng/mL TNFa or 100μM H2O2. RT-PCR and Western blot were used to detect Per2 expression. After two hours of treatment, mitochondrial membrane potential (ΔψM) was detected using JC1 fluorescence probe and mitochondrial respiration capacity was evaluated via Seahorse Mito Stress Test. After four hours of treatment, cell death was measured using Annexin V and propidium iodide (PI) apoptosis kit via flow cytometry.

Results: Per2 siRNA significantly reduced Per2 mRNA and protein levels in HCM. Increased cell death and decreased ΔψM were observed in HCM treated with TNFa or H2O2. Knockdown of Per2 potentiated TNFa-induced cell death, TNFa- or H2O2 -disrupted ΔψM, and TNFa- or H2O2- impaired mitochondrial maximal respiration.

Conclusion/Implication: Per2 knockdown increases apoptotic susceptibility and mitochondrial dysfunction in human cardiomyocytes exposed to TNFa or H2O2. Delivery of Per2 may serve as a promising therapeutic strategy to protect cardiomyocyte mitochondrial function during periods of stress, such as myocardial infarction, organ transplantation, and cardiac surgery.

NIH NHLBI-T35 Award
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Year in school: Class of 2026
Specialty interest: procedurally oriented
Biggest takeaway: Working in Dr. Wang's lab this summer was a very productive and rewarding experience. I was able to work on our project from initial stages doing background research to gathering and analyzing data to publishing an article. This experience has been formative in my understanding of the research process in medicine and the involved logistics. I also enjoyed further developing my lab skills and using advanced instruments to collect data.