CHRD 2022: Abstract & Poster Submission Form

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Presenter Status

- ○ Undergraduate Students
- ○ Masters Student
- ◉ PhD Student
- ○ Post-Doctoral Fellows
- ○ Residents
- ○ Non-Trainee

Research Category

- ◉ Basic Science
- ○ Clinical
- ○ Community Health / Policy

Role in the project

- ☑ Design
- ☑ Perform Experiments
- ☑ Analyze Data
- ☑ Write Abstract
- ☐

Title

Sirtuin 3 (SIRT3) Prevents Doxorubicin Induced Dilated Cardiomyopathy: Investigating Mitochondrial Protein Acetylation, Cardiac Lipids and Metabolic Dysfunction

Background

Doxorubicin (DOX) is a chemotherapeutic used in the treatment of pediatric cancers but has dose-dependent cardiotoxic side effects. Previously we showed that DOX decreases expression of the mitochondrial lysine deacetylase, SIRT3 in the mouse heart.

Objective

We hypothesize that DOX impairs cardiac function and energy production via reduced SIRT3 expression and dysregulated mitochondrial protein acetylation. We further hypothesize that increased SIRT3 expression could attenuate DOX-induced cardiac dysfunction by altering acetylation of enzymes involved in lipid remodeling and metabolic processes.

Methods

Mice expressing cardiac restricted full length M1-SIRT3 (mitochondrial localized), and short M3-SIRT3 (lacking localization signal) received saline or DOX injections of 8 mg/kg body weight for 4 weeks and were compared to non-transgenic (Non-Tg) littermates. Transthoracic echocardiography was performed on all mice (n=10). Total cardiac lipids were isolated from DOX treated cardiac tissue by chloroform:methanol extraction and global lipid analysis was performed by QTRAP LC-MS/MS (n=6). Cardiac mitochondria were isolated, and an anti-acetylated lysine antibody was used to enrich for tryptic digested peptides containing Acetyl-K and analyzed by QTRAP LC-MS/MS (n=6).

Results

DOX reduced left ventricular posterior wall thickness and ejection fraction dysfunction in Non-Tg mice, while increased expression of M1-SIRT3 and M3-SIRT3 transgenes preserved these cardiac parameters ($P<0.05$) following DOX treatment. Triglycerides were decreased in DOX treated hearts while phosphatidylserine, sphingomyelin (SM) and ganglioside (GM3) lipid species were increased ($p<0.05$). A negative correlation between decreased cardiac output and increased GM3 24:1 ($R=-0.62$, $P<0.05$), PS 38:4 levels ($R=-0.81$, $P<0.005$) and SM 35:1 ($R=-0.65$, $P<0.05$) was identified. We identified 150 differentially acetylated peptides ($p<0.05$) involved in metabolic processes (eg. IDH2, HADHA, $P<0.05$). M1-SIRT3 expression restored peptide acetylation in the heart.

Conclusion

Increased SIRT3 expression in the heart rescued DOX-induced cardiac dysfunction. DOX-induced cardiac dysfunction involved alterations in cardiac lipids and acetylated proteins that could be restored by increased SIRT3 expression in the heart.

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