CHRD 2021: Abstract & Poster Submission Form

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Research Category:

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

What was your role in the project?

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

Presenter Status:

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

Title

Sirtuin 3 Attenuates Doxorubicin Induced Cardiac Dysfunction by Regulating the Mitochondrial Acetylome and Alterations of the Cardiac Lipidome

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 through reduced SIRT3 and altered mitochondrial acetylation. We further hypothesize that increased SIRT3 expression could attenuate DOX-induced cardiac dysfunction via alterations of protein acetylation to 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 caused cardiac dysfunction in Non-Tg mice. Expression of M1-SIRT3 and M3-SIRT3 transgenes preserved left ventricular posterior wall thickness ($P<0.05$) and ejection fraction ($P<0.05$) in DOX treated mice. Triglycerides and phospholipids (PE, PI) 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. DOX increased the acetylation of 36 peptides ($p<0.05$) involved in metabolic processes (eg. IDH2, HADHA, $P<0.05$) while M1-SIRT3 expression reduced peptide acetylation.

Conclusion

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

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- For each author, please click "**[+] Add Item**" and provide the author's information

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