ABSTRACT SUBMISSION FORM

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Exploring the role of sex and gender on health research

CHRD
CHILD HEALTH RESEARCH DAYS

CHRD 2020: Abstract Submission Form

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Title
SIRT3 Attenuates Doxorubicin Induced Cardiotoxicity by Regulating the Mitochondrial Acetylome and Cardiac Lipidome

Background
Doxorubicin (DOX) is a chemotherapeutic with dose-dependent cardiotoxic effects that limits its use in patients. 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 lipid remodeling and alterations of protein acetylation to improve metabolic processes.

Methods
Mice expressing cardiac restricted full length M1-SIRT3 (mitochondrial localized), and truncated M3-SIRT3 (lacking localization signal) received saline or DOX injections of 8 mg/kg body weight for 4 weeks and compared to non-transgenic (Non-Tg) littermates. Transthoracic echocardiography was performed on all mice (n=10 per group). 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 from all mouse groups 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
Expression of M1-SIRT3 and M3-SIRT3 transgenes in the heart preserved left ventricular posterior wall thickness ($P<0.05$) and ejection fraction ($P<0.05$) in DOX treated mice. Global lipidomics analysis of DOX treated mouse hearts showed decreased triglycerides and phospholipids (PE, PI, PC) while increases in sphingomyelin and phosphatidylserine (PS) lipid species ($p<0.05$). Specifically, a negative correlation

between ejection fraction and PS 38:4 levels (R2=0.76, P<0.0005) and a positive correlation with PI 36:4 levels (R2=0.78, P<0.0005) was found. Acetylated peptides of proteins involved in metabolic processes, oxidative stress resistance and lipid remodelling (eg. IDH2, SOD2, HADHA, P<0.05) were enriched in DOX-treated mice.

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.

Theme:
Basic Science

Do you have a table/figure to upload?
No

Are you willing to participate in Goodbear's Den?
Yes

Presenter Status:
PhD Student

What was your role in the project?
Perform experiments, Analyze Data and Write Abstract

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