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

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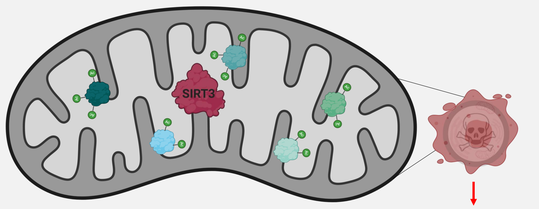
INTRODUCTION

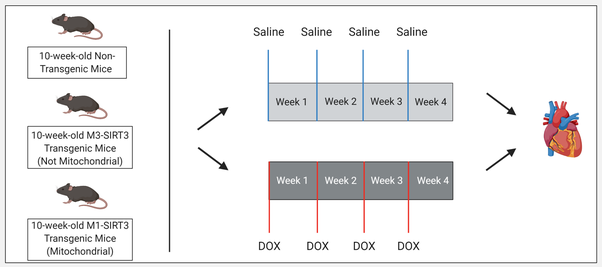
- Doxorubicin (DOX) is a chemotherapeutic with dose-dependent cardiotoxic effects that limits its use in patients.
- Sirtuins (SIRT) are a class of lysine deacetylases. SIRT3 is the main mitochondrial lysine deacetylase which regulates mitochondrial proteins.
- Previously we showed that DOX decreases expression of SIRT3 in H9c2 rat cardiomyocytes and in the mouse heart.
- Down regulation of SIRT3 with DOX treatment results in an increase in mitochondrial protein acetylation.
- SIRT3 overexpression in H9c2 rat cardiomyocytes prevents DOX induced mitochondrial dysfunction.



HYPOTHESIS

Increased SIRT3 expression in vivo could attenuate DOX-induced cardiac dysfunction via alterations of protein acetylation to enzymes involved in lipid remodeling and metabolic processes

ANIMAL MODEL



Mice with cardiac restricted expression of full length (M1SIRT3) which is localized to the mitochondria or truncated (M3-SIRT3) which lacks the mitochondrial localization signal by muscle creatine kinase (MCK) and myosin-heavy chain (MHC) promoters respectively were treated with DOX.

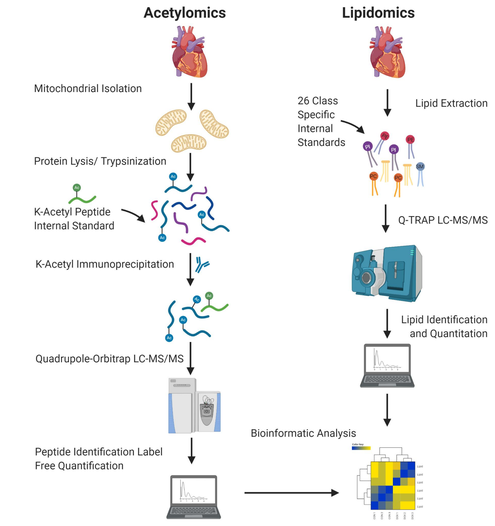
STATISTICS

Statistics are Student's T-Test or Two-way ANOVA with Tukey Post-Hoc Analysis. Data represented as mean ± SEM unless otherwise indicated. P-values indicated multiple comparisons shown on graph. * p<0.05 in comparison to control group.

The Children's Hospital Research Institute of Manitoba

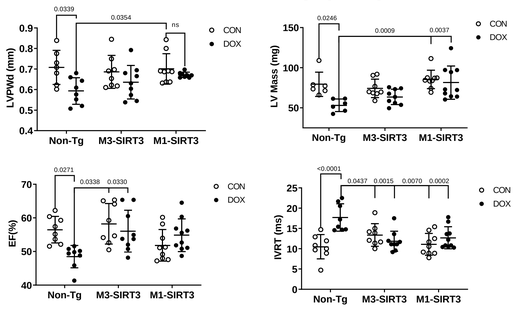
CHILD HEALTH RESEARCH DAYS

EXPERIMENTAL METHODS

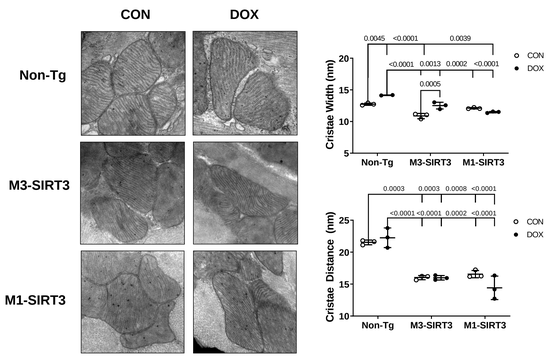


RESULTS

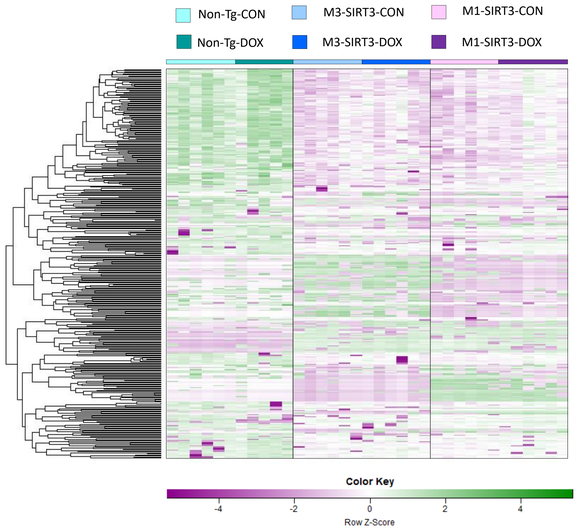
1. Mitochondrial M1-SIRT3 Expression Prevents DOX-induced Dilated Cardiomyopathy



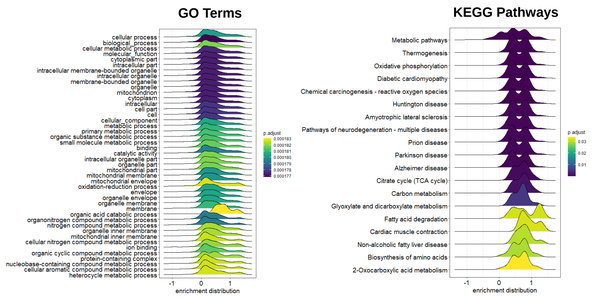
2. DOX Induces Changes to Mitochondrial Ultrastructure and SIRT3 Expression Alters Mitochondria Cristae



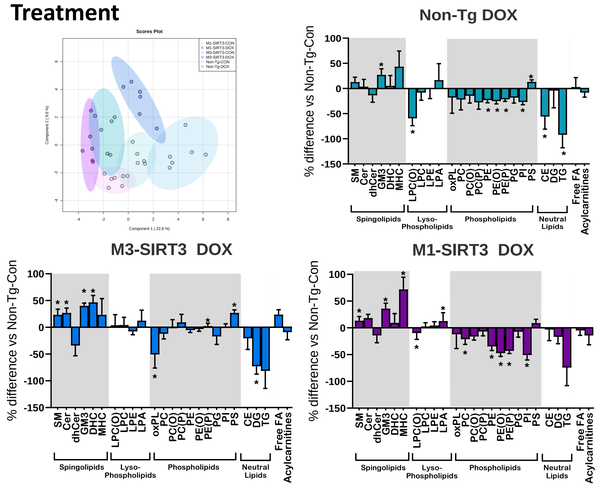
3. DOX Alters Acetylation of Mitochondrial Enzymes. SIRT3 Prevents DOX-induced Changes to Acetylation



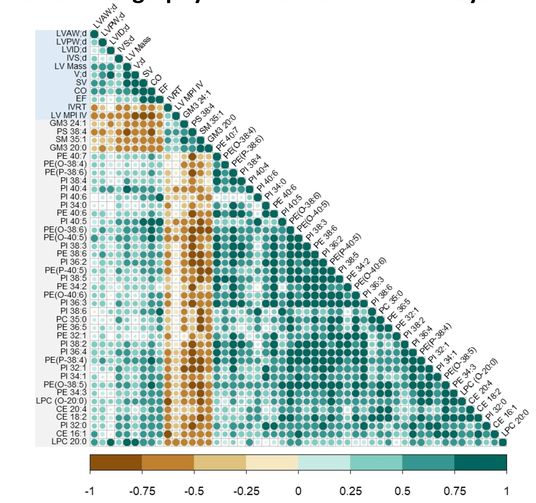
4. DOX Induces Differential Acetylation of Proteins Involved in Cardiac Energy Production and Fatty Acid Metabolism.



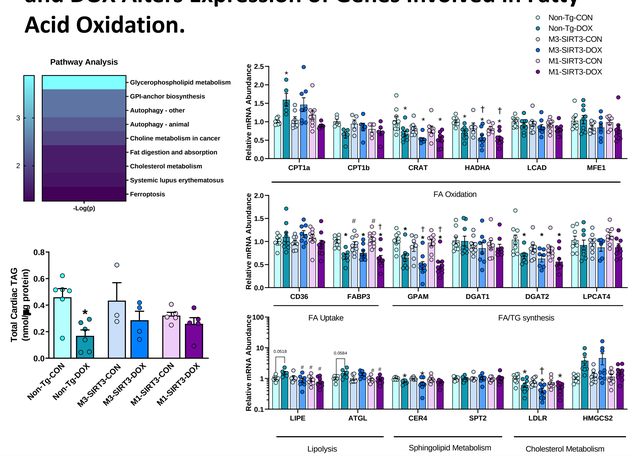
5. Characterization of Cardiac Levels as Result of DOX Treatment



6. Correlation of Altered Lipid Signatures with Echocardiography Parameters of Cardiac Dysfunction



7. SIRT3 Prevents DOX-induced Decreases in Triglycerides and DOX Alters Expression of Genes Involved in Fatty Acid Oxidation.



CONCLUSION

- DOX reduced SIRT3 which altered acetylation of proteins involved in cardiac energy production and fatty acid metabolism
- Increased SIRT3 expression in the heart rescues DOX induced cardiac dysfunction and prevents increases in acetylation
- DOX induced alterations in cardiac lipids which correlated with the dilated cardiomyopathy phenotype
- SIRT3 prevents decreases in cardiac triglycerides. DOX decreases genes involved in cardiac energy production
- SIRT3 could be a potential therapeutic target for the treatment of chemotherapy induced cardiac dysfunction

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CIHR IRSC Canadian Institutes of Health Research / Instituts de recherche en santé du Canada