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CARDIAC SIRT3 ATTENUATES DOXORUBICIN-INDUCED CARDIAC DYSFUNCTION IN RODENTS

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Background:
Doxorubicin (DOX) is an effective chemotherapeutic, but it has dose-dependent cardiotoxic effects that limits its use in pediatric patients. Previously our lab has shown that DOX decreases expression of the mitochondrial lysine deacetylase SIRT3 and mitochondrial phospholipid cardiolipin (CL) in the mouse heart.

Objective:
We hypothesize that DOX impairs cardiac function and energy production as a consequence of reduced SIRT3 expression and CL levels and DOX-induced cardiac dysfunction can be attenuated by increasing SIRT3 expression.

Methods:
Mice expressing full length M1-SIRT3 (mitochondrial localized), and truncated M3-SIRT3 (lacking localization signal) were used in these studies. Mice were given saline or DOX injections of 8.0mg/kg body weight for 4 weeks and compared to non-transgenic littermates. Transthoracic echocardiography was performed on all mice (n=10 per group) and parameters of cardiac structure, systolic and diastolic function were measured. Cardiac mitochondria were isolated from saline and DOX non-transgenic mice and an anti-acetylated lysine antibody was used to enrich for tryptic digested peptides containing acetylated lysines and analyzed by mass spectroscopy.

Results:
DOX decreased left ventricular posterior wall thickness compared to controls ($P<0.05$), while increased M1-SIRT3 and M3-SIRT3 expression prevented cardiac remodelling. DOX reduced ejection fraction and increased intraventricular relaxation time in non-transgenic mice ($P<0.05$). SIRT3 transgenic expression in the heart conferred resistance to DOX-induced functional impairments of the heart ($P<0.05$). Quantitative PCR of cardiolipin biosynthesis genes revealed *Ptpmt1* and *Crls1* gene expression was reduced by half with DOX compared to controls ($p<0.01$). In the DOX mice, an enrichment of peptides containing acetylated peptides was observed in proteins involved in metabolic and CL remodelling processes in cardiac mitochondria (eg. ATP5F1A, TFEα, $P<0.05$, >2-fold increase).

Conclusion:
Increased SIRT3 expression in the heart rescues DOX-induced cardiac dysfunction. DOX-induced cardiac dysfunction could be explained by alterations in the mitochondrial acetylome.