Poster Number 3

Abstract 0240_0346_000046

Cardiac SIRT3 Attenuates Doxorubicin-Induced Alterations of the Mitochondrial Acetylome and Cardiac Dysfunction in Rodents

Mateusz Tomczyk, CHRIM, University of Manitoba; **Bo Xiang**, CHRIM, University of Manitoba; **Stephanie Kereliuk**, CHRIM, University of Manitoba; **Kyle Cheung**, CHRIM, University of Manitoba; **Vernon Dolinsky**, CHRIM, University of Manitoba

Background:

Anthracyclines such as doxorubicin (DOX) are effective chemotherapeutics, but have limited application due to dose-dependent, cardiotoxic effects. Sirtuins are a class of lysine deacetylases that remove acetyl-groups from histones, proteins and metabolites. Previously our lab has shown that the expression of the mitochondrial Sirtuin 3 (SIRT3) is downregulated by DOX in the mouse heart.

Objective:

We hypothesize that DOX increases mitochondrial protein acetylation via reduced SIRT3 expression and cardiac function in mice can be improved by increasing SIRT3 expression following treatment with DOX.

Methods:

Mice expressing full length (M1-SIRT3) by the muscle creatine kinase promoter, and truncated (M3-SIRT3) by the alpha-myosin heavy chain promoter were used in this study and compared to non-transgenic mice. Mice were given DOX injections of 8.0mg/kg body weight for 4 weeks while controls received an equal volume of saline. Transthoracic echocardiography was performed on all mice (n=6 per group). Parameters of cardiac structure (e.g. left ventricular posterior wall thickness and internal dimensions), systolic and diastolic function (e.g. ejection fraction and intraventricular relaxation time, respectively) were measured. Mitochondria were isolated from the heart and tryptic digested peptides enriched for lysine acetylation with an anti-acetylated lysine antibody, were used for mass spectrometric analysis.

Results:

DOX decreased left ventricular posterior wall thickness and intraventricular sepal thickness compared to controls ($P<0.05$), while 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 transgene expression in the heart conferred resistance to DOX-induced functional impairments and maintained normal ejection fraction and intraventricular relaxation time ($P<0.05$). Initial mass spectroscopy data shows enrichment of acetylated peptides from metabolic enzymes in cardiac mitochondria.

Conclusion:

Increased SIRT3 expression in the heart rescues DOX-induced cardiac dysfunction. Future mass spectrometric analysis will reveal how DOX alters mitochondrial protein acetylation and affects cardiac function