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Analysis of the Role of ATPase Inhibitory Factor 1 (IF1) in Doxorubicin-Induced Cardiotoxicity

Background: ATPase Inhibitory Factor 1 (IF1) is a nuclear-encoded ATP synthase-interacting mitochondrial protein. IF1 is known to be upregulated during periods of elevated stress, such as during myocardial infarctions or cardiac hypertrophy. Previously conducted lab research has demonstrated that mice with the absence of the protein IF1 were protected against pathological cardiac hypertrophy. To further investigate the extent of such findings, an experiment was designed to investigate the role of the IF1 protein in cardiotoxic conditions induced by Doxorubicin (DOX), a widely used anti-cancer drug. DOX is known to induce cardiotoxicity through the generation of reactive oxygen species, increased levels of lipid peroxidation, and mitochondrial dysfunction. Doxorubicin-induced cardiomyopathy is associated with a low prognosis and can serve to be fatal in certain populations. We hypothesized that mice with the absence of IF1 will demonstrate more preserved cardiac functions in the presence of DOX.

Methods: To test the hypothesis, DOX was intraperitoneally injected into two separate groups of mice: mice for which the IF1 protein was knocked out (IF1-KO) and wildtype mice normally expressing the IF1 protein (IF1-WT). The drug was dissolved in a solvent consisting of dimethyl sulfoxide (DMSO), PEG-300, Tween-80, and distilled water in pre-designated proportions. Injections were performed on three separate days with 6 mg/kg of DOX administered on each injection day. Injections were conducted on Day 0, Day 2, and Day 4. Control mice were injected simply with solvent. Subsequently, transthoracic echocardiograms were performed using a VEVO F2 system at one-week intervals for three weeks i.e. Day 7, Day 14, and Day 21. Long-axis M-Mode images were obtained to analyze systolic parameters: ejection fraction, fractional shortening, left ventricular mass, as well as left ventricle anterior and posterior wall thickness. Body mass was also measured initially and after the three-week interval.

Results: Findings demonstrated that in the presence of DOX, ejection fraction and fractional shortening, the two parameters of cardiac contraction, significantly decreased in IF1-WT mice; whereas no significant decrease was seen in IF1-KO mice. Furthermore, left ventricular anterior wall thickness was found to be significantly reduced in both IF1-WT and IF1-KO mice, suggesting that DOX may lead to a decrease in heart size.

Conclusions: These results demonstrate that the absence of IF1 may provide protection against the cardiotoxic effects of DOX, thus supporting the hypothesis. Further studies could investigate the role of increased doses of DOX on cardiac physiology as well as the effects of increased time intervals through the performance of transthoracic echocardiograms after five to seven weeks. Future experiments using other pathophysiological and biochemical methodologies will gain further insights into the mechanisms of the protective effects of eliminating IF1. Experimental findings may yield new insights into the development of interventions to mitigate adverse effects of this drug in cancer patients under chemotherapy treatments.