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"Implications of Kynurenic Acid in preventing Doxorubicin induced cardiotoxicity"

Doxorubicin (DOX) is a widely used chemotherapeutic agent for treating various cancers, including breast cancer, lymphomas, and leukemias. Despite its efficacy, DOX is associated with severe cardiotoxicity, leading to heart failure and other cardiovascular complications. Previous studies have shown that one of the main targets of this toxicity is mitochondrial dysfunction via impairing mitochondrial membrane potential, decreasing ATP storage, increasing Reactive oxygen species (ROS) etc. As the mitochondria makes up one third of the volume of the heart it can be a potential target for therapeutic intervention. Many reports showed that Mitochondrial protein ATPase inhibitory factor 1 (IF1) can stop ATP hydrolysis and ultimately increasing ATP storage. This study aims to investigate the role of IF1 in mitigating the mitochondrial toxicity induced by DOX.

In order to evaluate IF1 mediated cardio protection in the mitochondria, first AC-16 (human cardiomyocytes) cells were transduced with IF1 overexpression (OE), IF1 dominant negative E55A (DN), and a null vector as a viral internal control with MOI 100. 24 hours post transduction, the cells were exposed to 2.5 μM of DOX for 24 hours. Cell viability was assessed using the MTT and cellular impedance assays. Mitochondrial function was evaluated using the Seahorse XF24 analyzer and mitochondrial membrane potential was assessed using the TMRE assay.

Experimental results did show a significant decrease in mitochondrial maximal respiration and a significant increase in ATP production due to IF1 DN group compared to OE group. TMRE analysis did not indicate a significant difference in membrane potential between any of the groups. Furthermore, MTT and cellular impedance assays revealed no significant differences in cell viability between the groups in response to DOX exposure.

The findings of this study suggest that IF1 knockout can potentially enhance mitochondrial function and preserve more ATP under DOX stress. Further studies should investigate the effect of IF1 on mitochondrial membrane potential and free radical production in the mitochondria using more sensitive and precise methods. In addition, long term studies should be conducted to evaluate the cardioprotective effects of IF1 under chronic DOX exposure. In conclusion, IF1 can be regarded as potential therapeutic target for alleviating DOX-induced mitochondrial impairment and ultimately improve heart function in cancer patients.