Activation of CISD2 as a protective strategy against doxorubicin-induced cardiotoxicity

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Background: Cardiotoxicity of doxorubicin, a chemotherapy medication, remains the most dangerous side effect. CISD2 plays a critical role during cardiac aging.
Objectives: We use a potent CISD2 activator, hesperetin, to ameliorate doxorubicin-induced cardiotoxicity by upregulating CISD2 in mice.
Methods: Two animal models, an acute and a tumor-bearing doxorubicin-induced cardiotoxicity model, were used in this study. Both genetic and pharmacological approaches were employed. Transgenic mice and a potent CISD2 activator, hesperetin, were utilized to ameliorate doxorubicin-induced cardiotoxicity by upregulating CISD2 expression in mice. Additionally, a human-derived iPSC system was used to provide human-relevant evidence. Comprehensive biological, histological, transcriptomic, and metabolomic analyses were conducted.
Results: Five findings are pinpointed. Firstly, doxorubicin suppresses Cisd2 expression resulting in cardiac electromechanical dysfunction. Intriguingly, transgenic overexpression of Cisd2 mitigates doxorubicin-induced cardiotoxicity. Secondly, hesperetin effectively sustains a high level of Cisd2 and improves cardiac function in a Cisd2-dependent manner after doxorubicin treatment. Importantly, hesperetin doesn't influence the anti-cancer efficacy of doxorubicin. Thirdly, doxorubicin downregulates the transcription of CISD2 by decreasing the expression of two transcription regulators, TAF1 and TCF12. Fourthly, analysis of transcriptomic and metabolomic datasets reveals that hesperetin protects the heart via a network connecting glucose, fatty acids and amino acids metabolism, thereby ensuring a sufficient energy supply. Additionally, hesperetin improves antioxidation capacity via reinstating the pentose phosphate and glutathione pathways. Finally, in human iPSC-derived cardiomyocytes, hesperetin significantly upregulates CISD2 and protects the cells from doxorubicin-induced toxicity and functional damage.