Protective role of an NAD^+-dependent deacetylase SIRT1 in doxorubicin-induced cardiotoxicity.

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Background: Doxorubicin (DOX) is an anti-cancer drug which develops heart failure. SIRT1, an NAD^+-dependent deacetylase, affords cellular protection under various stresses. Here, we investigated whether and how SIRT1 protects the heart from DOX-induced cardiotoxicity in mice.

Methods and Results: Wild type (WT) and tamoxifen-inducible cardiomyocyte-specific SIRT1 knockout (cKO) mice were treated with vehicle (Veh) or DOX (4 IP injections of 5 mg/kg/week) starting at 3 months of age. Echocardiography at 1 week after final vehicle or DOX showed that left ventricular fractional shortening (FS), an index of cardiac function, was similar in vehicle treated WT and cKO. Although DOX reduced FS in both genotypes, cKO showed lower FS after DOX than that in WT. Cardiac ANP mRNA level was also higher in cKO than WT after DOX. TUNEL-positive nuclei were unchanged in Veh-treated but were more increased by DOX in cKO than WT, indicating increased apoptosis in cKO after DOX. A long-range PCR method for analysis of mtDNA deletion, which indicates mtDNA damage, demonstrated an increase in level of mtDNA with deletion by DOX in cKO but not in WT. Immunoblotting showed that DOX significantly reduced cardiac levels of an autophagosome marker LC3-II and p62 protein which is degraded by autophagy in WT but not in cKO, suggesting activation of cardiac autophagy only in WT.

Conclusions: SIRT1 deletion worsens DOX-induced cardiotoxicity probably through enhanced mitochondrial damage via impaired autophagy.