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RAC1 SIGNALLING MEDIATES DOXORUBICIN-INDUCED CARDIOTOXICITY THROUGH BOTH REACTIVE OXYGEN SPECIES DEPENDENT AND INDEPENDENT PATHWAYS

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Objectives Doxorubicin causes damage to the heart, often leading to irreversible cardiomyopathy, which is fatal. Reactive oxygen species (ROS) or oxidative stress is involved in cardiomyocyte death, contributing to doxorubicin-induced cardiotoxicity. This study was to investigate the role of Rac1, an important subunit of NADPH oxidase in doxorubicin-induced cardiotoxicity and the underlying mechanisms.

Methods The models of doxorubicin-induced cardiotoxicity were created by challenging the mice with 20 mg/kg doxorubicin intraperitoneally. Cardiac function was determined by hemodynamic measurements. Cardiomyocytes apoptosis was assayed by caspase-3 activity assay and DNA fragmentation ELISA. ROS production

was measured using DCF-DA molecule probe and NADPH oxidase was measured by an assay kit. We also used a HDAC assay kit to measure HDAC activity of cardiomyocytes.

Results In a mouse model of acute doxorubicin-induced cardiotoxicity, cardiomyocyte-specific deletion of Rac1 inhibited NADPH oxidase activation and ROS production, prevented cardiac cell death and improved myocardial function in Rac1 knockout mice. Therapeutic administration of a specific Rac1 inhibitor NSC23766 achieved similar cardioprotective effects of Rac1 inhibition in doxorubicin-stimulated mice. In vitro studies using rat cardiomyoblasts H9c2 cells and neonatal mouse cardiomyocytes demonstrated that Rac1 inhibition attenuated apoptosis as determined by decreases in caspase-3 activity and DNA fragmentation in response to doxorubicin, which correlated with a reduction of ROS production and down-regulation of p53 acetylation and histone H2AX phosphorylation. Doxorubicin also inhibited the activity of classical histone deacetylases (HDAC), which was preserved by Rac1 inhibition. Interestingly, scavenging ROS mitigated apoptosis but did not change HDAC activity and p53 acetylation stimulated by doxorubicin, suggesting both ROS dependent and independent pathways are involved in Rac1-mediated cardiotoxicity. Furthermore, HDAC inhibitor trichostatin A enhanced apoptosis, p53 acetylation and H2AX phosphorylation in doxorubicin-treated cardiomyocytes.

Conclusions Rac1 signalling contributes to doxorubicin-induced cardiotoxicity through both ROS dependent mechanism and ROS independent HDAC/p53 signalling in cardiomyocytes. Thus, inhibition of Rac1 may be a useful therapy for doxorubicin-induced cardiotoxicity.