cytes. To evaluate the role of TOP2β and activation of the DNA damage response compared with doxorubicin-induced DSBs and cell death. After 72 hours of exposure to doxorubicin, genes required for mitochondrial biogenesis and oxidative phosphorylation were selectively repressed in wild-type cardiomyocytes, suggesting a mechanism by which doxorubicin might exert negative effects on mitochondria in the presence of TOP2β. Indeed, mitochondrial membrane potential and oxygen consumption were compromised, and structural damage and reactive oxygen species generation were increased in wild-type cardiomyocytes compared with their Top2b-null counterparts. Chronic doxorubicin exposure also increased end systolic and end diastolic volumes and reduced ejection fraction in wild-type mice but not Top2b-null mice, further indicating that the harmful effects of doxorubicin on cardiac function require TOP2β. These findings suggest that high expression of TOP2β in cardiomyocytes may be a predictive biomarker for doxorubicin-induced cardiotoxicity and that anticancer agents that selectively target TOP2α may be less cardiotoxic.

Topoisomerase IIβ Mediates Doxorubicin-Induced Cardiotoxicity


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