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DDX3X alleviates doxorubicin-induced cardiotoxicity by regulating Wnt/β-catenin signaling pathway in an in vitro model

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Abstract

The life-threatening adverse effects of doxorubicin (Dox) caused by its cardiotoxic properties limit its clinical application. DDX3X has been shown to participate in a variety of physiological processes, and it acts as a regulator of Wnt/β-catenin signaling. However, the role of DDX3X in Dox-induced cardiotoxicity (DIC) remains unclear. In this study, we found that DDX3X expression was significantly decreased in H9c2 cardiomyocytes treated with Dox. *Ddx3x* knockdown and RK-33 (DDX3X ATPase activity inhibitor) pretreatment exacerbated cardiomyocyte apoptosis and mitochondrial dysfunction induced by Dox treatment. In contrast, *Ddx3x* overexpression ameliorated the DIC response. Moreover, Wnt/β-catenin signaling in cardiomyocytes treated with Dox was suppressed, but this suppression was reversed by *Ddx3x* overexpression. Overall, this study demonstrated that DDX3X plays a protective role in DIC by activating Wnt/β-catenin signaling.

KEYWORDS
apoptosis, cardiotoxicity, DDX3X, doxorubicin, Wnt/β-catenin

1 | INTRODUCTION

Doxorubicin (Dox) is a highly effective antineoplastic agent against various malignancies, such as lung cancer, breast cancer, leukemia, and lymphoma.[1,2] However, the cardiotoxic side effects of Dox, including acute and chronic dose-dependent cardiotoxicity and heart failure, limit its clinical application.[3] A number of factors participate in the pathogenesis of Dox-induced cardiotoxicity (DIC), including oxidative stress, apoptosis, and intracellular calcium dysregulation.[4] However, the underlying mechanisms remain largely unknown.

Abbreviations: ANOVA, analysis of variance; CCK-8, cell counting Kit-8; DIC, dox-induced cardiotoxicity; Dox, doxorubicin; PVDF, polyvinylidene difluoride; qRT-PCR, quantitative real-time polymerase chain reaction; ROS, reactive oxygen species; SDS-PAGE, sodium dodecylsulfate-polyacrylamide gel electrophoresis.