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Long noncoding RNA NONMMUT015745 inhibits doxorubicin-mediated cardiomyocyte apoptosis by regulating Rab2A-p53 axis

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Doxorubicin (DOX) is an efficacious and widely used drug for human malignancy treatment, but its clinical application is limited due to side effects, especially cardiotoxicity. Our present study revealed that DOX could induce apoptosis in cardiomyocytes. Herein, we screened the dysregulated long noncoding RNAs (lncRNAs) in DOX-treated cardiomyocytes. Notably, overexpression of lncRNA NONMMUT015745 (lnc5745) could alleviate DOX-induced cardiomyocyte apoptosis both in vitro and in vivo. Conversely, silencing lnc5745 promotes cardiomyocyte apoptosis. Moreover, Rab2A, a direct target of lnc5745, possesses a protective effect in DOX-induced cardiotoxicity once knocked down. Importantly, we verified that the p53-related apoptotic signalling pathway was responsible for the lnc5745-mediated protective role against DOX-induced cardiomyocyte apoptosis. Mechanistically, Rab2A interacts with p53 and phosphorylated p53 on Ser 33 (p53 (Phospho-Ser 33)), promotes p53 phosphorylation, thereby activating the apoptotic pathway. Taken together, our results suggested that lnc5745 protects against DOX-induced cardiomyocyte apoptosis through suppressing Rab2A expression, modifying p53 phosphorylation, thereby regulating p53-related apoptotic signalling pathway. Our findings establish the functional mode of the lnc5745-Rab2A-p53 axis in DOX-induced cardiotoxicity. The development of new strategies targeting the lnc5745-Rab2A-p53 axis could attenuate DOX-induced cardiotoxicity, which is beneficial to its clinical anti-tumour application.

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INTRODUCTION

Doxorubicin (DOX), also known as Adriamycin, is a first-line anthracycline group of antibiotics that has been widely used as an efficacious chemotherapeutic for human malignancies, including solid sarcomas, breast carcinomas, haematological malignancies and soft tissue sarcomas, since the late 1960s [1, 2]. However, the clinical use of DOX is limited due to severe dose-dependent and cumulative cardiotoxicity [3]. Increasing the dosage of DOX will cause irreversible myocardial damage and ultimately lead to dilated cardiomyopathy (DCM) and congestive heart failure [4, 5]. Therefore, a thorough comprehension of the pathogenesis of DOX cardiomyopathy and the recognition of novel therapeutic targets for protecting cardiac function are urgently needed.

Recent studies have shown that the molecular mechanism responsible for the cardiotoxicity of DOX appears to be multifactorial [6]. Excessive ROS can induce oxidative damage to biological macromolecules, including DNA, proteins and lipids, and destroy the integrity and function of cell membranes [7–9]. Moreover, DOX-induced oxidative stress can directly induce cardiomyocyte apoptosis through multiple apoptotic pathways, leading to severe cardiac dysfunction. In addition, DOX can also evoke apoptosis in a non-ROS- and oxidative stress-dependent manner [10]. Our recent studies have demonstrated that inhibition of cardiomyocyte apoptosis can significantly attenuate DOX-induced cardiac dysfunction [11]. Therefore, a thorough comprehension of the pathogenesis of DOX-induced cardiomyocyte apoptosis and the recognition of novel therapeutic targets for protecting cardiac function are urgently needed.

Long noncoding RNAs (lncRNAs) are an important class of noncoding transcripts more than 200 nucleotides in length that lack functional open reading frames [12, 13] and thus do not code for proteins [14]. Increasing evidence shows that lncRNAs participate in the regulation of life events through multiple mechanisms, including epigenetic regulation, genomic imprinting, protein modification, RNA stability and RNA alternative splicing [15, 16]. LncRNAs are involved in the regulation of cardiac functions, such as cardiac growth and morphogenesis [17], electrical signal propagation and myocardial contraction [18, 19]. Previous findings have clarified that lncRNAs are powerful controllers of DCM, heart failure (HF) and myocardial infarction (MI) by regulating cardiomyocyte necrosis, necroptosis, and autophagy [20]. However, detailed studies on the influence

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