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Silibinin eliminates mitochondrial ROS and restores autophagy through IL6ST/JAK2/STAT3 signaling pathway to protect cardiomyocytes from doxorubicin-induced injury

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ABSTRACT

Growing evidence indicates that silibinin (SLB), a main component extracted from Chinese herb *Silybum marianum*, can effectively antagonize doxorubicin (DOX) induced myocardial injury (DIMI), but the specific molecular mechanism is still unelucidated. Herein, DOX induced human AC16 cardiomyocyte injury model and Network Pharmacology are used to predict and verify the potential mechanism. The analysis results of the core PPI network of SLB against DIMI show that JAK/STAT signaling pathway and autophagy are significantly enriched. Molecular docking results indicate that SLB has stronger binding ability to signaling key proteins IL6ST, JAK2 and STAT3 (affinity ≤ -7.0 kcal/mol). The detection results of pathway activation and autophagy level demonstrate that SLB significantly alleviates DOX induced IL6ST/JAK2/STAT3 signaling pathway inhibition and autophagy inhibition, reduces the death rate of cardiomyocytes. This protective effect of SLB is eliminated when key pathway proteins (IL6ST, JAK2, STAT3) are knocked down or autophagy is inhibited (3-MA or Beclin1 knockdown). These results suggest that the regulation of IL6ST/JAK2/STAT3 signaling pathway and autophagy may be important mechanism for SLB's protective effect on DOX injured cardiomyocytes. Further experimental results prove that knockdown of IL6ST, JAK2 and STAT3 eliminate the mitochondrial ROS scavenging effect and autophagy promoting effect of SLB. In sum, SLB can decrease the mitochondrial ROS and restore autophagy to antagonize DOX-induced cardiomyocyte injury by activating IL6ST/JAK2/STAT3 signaling pathway.

1. Introduction

Doxorubicin (DOX), as a representative drug of anthracycline, is commonly used to treat a variety of clinical malignant tumors. However, the clinical use of DOX is often accompanied by severe side effects, especially to the heart (Todorova et al., 2020). A large number of studies show that DOX-mediated cardiotoxicity is associate with oxidative stress, mitochondrial dysfunction, iron accumulation, inhibition of topoisomerase activity and other mechanisms (Damiani et al., 2016). Although dexrazoxane (DEX) is currently the only drug that can be used clinically to prevent anthracyclines-induced myocardial toxicity (Ganatra et al., 2019; Kopp et al., 2019), its pre-treatment can't fully

Abbreviations: SLB, silibinin; DOX, doxurubicin; DEX, dexrazoxane; IL6ST, interleukin-6 signal transducer; JAK2, Janus kinase 2; STAT3, signal transducer and activator of transcription3; MTT, 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide; LDH, lactate dehydrogenase; DMEM, Dulbecco's Modified Eagle Medium; FBS, fetal bovine serum; ROS, reactive oxygen species; PBS, phosphate-buffered saline; DIMI, doxorubicin induced myocardial injury; PPI, protein-protein interaction.

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