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# Doxorubicin-Induced Cardiotoxicity May Be Alleviated by Bone Marrow Mesenchymal Stem Cell-Derived Exosomal lncRNA via Inhibiting Inflammation

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## Abstract

**Purpose:** To explore the therapeutic mechanism of bone marrow mesenchymal stem cells derived exosomes (BMSC-Exos) for doxorubicin (DOX)-induced cardiotoxicity (DIC) and identify the long noncoding RNAs' (lncRNAs') anti-inflammation function derived by BMSC-Exos.

**Materials and methods:** High-throughput sequencing and transcriptome bioinformatics analysis of lncRNA were performed between DOX group and BEC (bone marrow mesenchymal stem cells derived exosomes coculture) group. Elevated lncRNA (ElncRNA) in the cardiomyocytes of BEC group compared with DOX group were confirmed. Based on the location and co-expression relationship between ElncRNA and its target genes, we predicted two target genes of ElncRNA, named cis_targets and trans_targets. The target genes were analyzed by enrichment analyses. Then, we identified the key cellular biological

pathways regulating DIC. Experiments were performed to verify the therapeutic effects of exosomes and the origin of lncRNAs in vitro and in vivo.

**Results:** Three hundred and one lncRNAs were differentially expressed between DOX and BEC groups (fold change >1.5 and $p < 0.05$), of which 169 lncRNAs were elevated in the BEC group compared with the DOX group. GO enrichment analysis of target genes of ElncRNAs showed that they were predominantly involved in inflammation-associated processes. KEGG analysis indicated that their regulatory pathways were mainly involved in oxidative stress-induced inflammation and proliferation of cardiomyocyte. The verification experiments in vitro showed that the oxidative stress and cell deaths were decreased in BEC groups. Moreover, from the top 10 ElncRNAs identified in the sequencing results, MSTRG.98097.4 and MSTRG.58791.2 were both decreased in the DOX group and elevated in BEC group. While in verification experiments in vivo, only the expression of MSTRG.58791.2 is consistent with the result in vitro.