Biomimetic nanozymes target the heart to suppress ferroptosis for ameliorating doxorubicin-induced cardiotoxicity via synergetic effect of antioxidant stress and Nrf2/Hmox1 inhibition

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Background: Doxorubicin (DOX) is the first-line standard treatment of numerous cancer. However, DOX may lead to irreversible degenerative cardiomyopathy, congestive heart failure, and various arrhythmias, known as doxorubicin-induced cardiotoxicity (DIC), which limits the clinical applications. Studies reported that ferroptosis plays an important role on the development of DIC. Targeted intervention of ferroptosis with the specific inhibitors, such as ferrostatin-1 (Fer-1), could effectively prevent DIC. In recent years, catalytic nanozymes, such as cerium oxide (CeO2), have received much attention due to their strong antioxidant properties.

Purpose: Our previous research found that the transferrin receptor (TfR) protein expression was significantly upregulated in DIC mice (Figure 1). In this study, we synthesized a biomimetic CeO2-based nanozyme by biomineralization with transferrin (Tf) proteins as the template, and then we assessed its targeted therapy for DIC via Tf-TfR mediated endocytosis.

Method: Cellular uptake, cytotoxicity test, intracellular mitochondrial membrane potential (MMP), reactive oxygen species (ROS), mitochondrial ferrous ions and lipid peroxidation toxicity were verified with rat cardiomyocytes line H9c2 cells. Afterward, the male C57BL/6N mice were randomly divided into control, DOX, DOX+Fer-1, and DM+NPs groups. Heart structure and function were measured by echocardiographic, electrocardiography and epicardial electrical labeling. Western blot determine mitochondrial homeostasis regulation-related proteins and Nrf2/Hmox1 signalling pathway. Finally, the biodistribution and biocompatibility of CeO2@TF was assessed.

Results: Transmission electron microscopy images revealed the encapsulated CeO2@TF was≈ 5 nm in diameter. The nanozyme significantly reversed cardiac structural and electrical remodeling and reduced myocardial necrosis. Meanwhile, RNA sequencing of ventricular tissue revealed increased cardiac Hmox1 mRNA levels in DIC mice (Figure 2). Further, it demonstrated that nanozyme intervention not only significantly suppressed the oxidative stress, mitochondrial lipid peroxidation and mitochondrial membrane potential damage, but also inhibited activation of Nrf2/Hmox1 signalling pathway to restore mitochondria-dependent ferroptosis. Furthermore, the nanozyme could be cleared by the hepatobiliary systems, and showed a good biocompatibility.

Conclusions: The current study showed that biomimetic mineralization of hybrid CeO2-based nanozyme against DIC were mediated by effect of antioxidant stress and the inhibition of Nrf2/Hmox1 signalling pathway, thereby maintaining mitochondrial homeostasis and function, and re-storing mitochondria-dependent ferroptosis. Furthermore, the nanozyme could be a promising prevention and treatment candidate for clinical translation as a novel cardiomyocyte ferroptosis protector to mitigate DIC and improve the prognosis and quality of life of cancer patients.