Biomineralized ceria nanoparticles target the heart to improve diabetic cardiac remodeling by regulating mitochondrial oxidative stress and decreasing excessive mitophagy

Q. Zhang1, Y. Zhang1, S. Cheng1, B. Xie1, Z. Zhou1, J. Peng1, Y. Zhang1, G. Tse1, Y. Zhao1, T. Liu1

12nd Hospital of Tianjin Medical University, Tianjin, China

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Background: An altered state of cardiomyocytes due to high glucose concentrations results in cell hypertrophy, leading to diabetic cardiomyopathy (DCM). The molecular regulatory process of mitochondrial dyshomeostasis and mitophagy, oxidative stress, and reactive oxygen species (ROS) production in diabetes is still not fully understood. Mitochondrial dyshomeostasis and mitophagy could be critical factors in the heart remodeling that occurs in diabetes.

Purpose: Our transcriptome sequencing of heart tissue revealed upregulation of the gene encoding the transferrin receptor (TfR) in the diabetic rat (Figure 1A). We then validated in vitro that high glucose increased TfR protein expression in the HL-1 cell line (Figure 1B). Herein, we developed a novel therapeutic ceria nanoparticle via biomineralization using transferrin (Tf) protein as a template and assessed its targeted therapy for DM-induced cardiac remodeling via Tf-TfR mediated endocytosis.

Method: We synthesized Tf protein-based ceria NPs (CeO2@Tf) via biomineralization. Then the physicochemical and biological properties of NPs were characterized. Cellular uptake, cytotoxicity test, intracellular mitochondrial membrane potential (MMP), and ROS were verified with mouse cardiomyocytes HL-1 cells line. Afterward, the male C57BL/6N mice were randomly divided into control, DM, DM+Metformin (Met), and DM+NPs groups with eight weeks of treatment. Heart structure and function were measured by echocardiographic. The heart tissues were stained with hematoxylin, eosin (H&E), and Masson's trichrome stain to observe morphological changes and fibrosis. Western blot was used to determine mitochondrial homeostasis regulation-related proteins and mitophagy pathway.

Results: TEM and X-ray photoelectron spectroscopy characterized the properties successfully. MTT assay shows that HL-1 cell viabilities were not influenced by CeO2@Tf at 200 µM. High-glucose treatment led to increased ROS and decreased intracellular MMP in HL-1 cells. DM mice cardiac transcriptome sequencing results showed upregulation of transferrin receptor gene expression. Echocardiographic showed increased LAD and abnormal diastolic and systolic functions. All these abnormal changes were improved in the DM+ Met and DM+NPs groups. Our investigations revealed proteins linked to the PINK1-Parkin signaling pathway (Figure 2A-B) and found that the level of mitophagy in the diabetic group was overly high, which was improved after the application of CeO2@Tf. We observed the mitochondrial autophagosomes through transmission electron microscopy (Figure 2C). The autophagosomes in the diabetic group increased significantly and improved after treatment with CeO2@Tf.

Conclusions: These consistent biochemical and histopathological results suggest that the biomimetic mineralization of CeO2@Tf could inhibit oxidative stress and improve mitochondrial function in vitro induced by high-glucose and in vivo caused by DM, alleviating cardiac remodeling in DM mice.