Contribution ID: **11** Type: **特邀报告**

Sustained release of ceria nanoparticles is a potential therapeutic for Friedreich’s ataxia by stabilizing iron sulfur clusters

Friedreich ataxia (FRDA) is a mitochondrial disease, characterized by neurodegeneration accompanied with hypertrophic cardiomyopathy and diabetes due to the deficiency of the protein frataxin (FXN). Mitochondrial dysfunction results directly from the lack of iron sulfur cluster biogenesis and indirectly from the oxidative stress caused by FXN insufficiency. In this study, silk fibroin-coated ultra-small ceria nanoparticles (SF@CeO2 NPs) were prepared, which combines the excellent enzyme-like activity resulting from ceria and the super-biocompatibility and sustained-release property of SF nanoparticles. Intriguingly, SF@CeO2 NPs administration for one month completely ameliorated the neuronal and cardiomyocyte impairment of FXN deficiency-induced FRDA in a mouse model, including all the tested phenotypes of neurological behavior and myocardial hypertrophy. Histologically and cytologically, the number and morphology of neurons and cardiomyocytes reversed to normal, associated with a great improvement of mitochondrial morphology and function in YG8R mice after treatment with SF@CeO2 NPs. Most importantly, the mechanistic investigations revealed that, in addition of its known antioxidant activity, ceria stabilized iron-sulfur clusters in FXN deficient tissues and cells, as well as in cell-free systems. This novel protective mechanism of SF@CeO2 NPs provides exciting potential for clinical application in FRDA and in other diseases with iron sulfur cluster deficiency.

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