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Ceria-zirconia nanoparticles reduce intracellular globotriaosylceramide accumulation and attenuate kidney injury by enhancing the autophagy flux in cellular and animal models of Fabry disease

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Objectives: Fabry disease (FD) is a lysosome storage disease (LSD) characterized by significantly reduced intracellular autophagy function. This contributes to the progression of intracellular pathologic signaling and can lead to organ injury. Phospholipid–polyethyleneglycol-capped Ceria-Zirconia antioxidant nanoparticles (PEG-CZNPs) have been reported to enhance autophagy flux. We analyzed whether they suppress globotriaosylceramide (Gb3) accumulation by enhancing autophagy flux and thereby attenuate kidney injury in both cellular and animal models of FD.

Methods: PEG-CZNPs were synthesized using a non-hydrolytic sol-gel reaction method. HK-2 cells and human podocytes were reverse transfected with α-galactosidase A (α-GLA) siRNA for cellular model for fabry disease. For in-vivo study 4-week-old male B6;129-Gla^{tm1Kul}/J mice were treated for 8 weeks with 10mg/kg of PEG-CZNPs twice per week via intraperitoneal injection. PCR, immunoblotting, immunoflouresce assay, flow cytometry, electron microscopy analysis, ICP-MS, LC/MS, biochemical and histological analysis were done.

Results: Gb3 was significantly increased in cultured human renal proximal tubular epithelial cells (HK-2) and human podocytes following the siRNA silencing of α galactosidase A (α-GLA). PEG-CZNPs effectively reduced the intracellular accumulation of Gb3 in both cell models of FD and improved both intracellular inflammation and apoptosis in the HK-2 cell model of FD. Moreover these particles attenuated pro fibrotic cytokines in the human podocyte model of FD. This effect was revealed through an improvement of the intracellular autophagy flux function and a reduction in reactive oxygen species (ROS). An FD animal model was generated in which 4-week-old male B6;129-Glatm1Kul/J mice were treated for 8 weeks with 10mg/kg of PEG-CZNPs (twice weekly via intraperitoneal injection). Gb3 levels were reduced in the kidney tissues of these animals, and their podocyte characteristics and autophagy flux functions were preserved.

Conclusions: PEG-CZNPs alleviate FD associated kidney injury by enhancing autophagy function and thus provide a foundation for the development of new drugs to treat of storage disease.