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Improving autophagy flux by TFEB activation via GSK3ß signaling pathway with PEG-CZNPs attenuated chronic kidney injury 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 accessed the action mechanisms of PEG-CZNPs in autophagy regulation and checked the effect on chronic kidney injury in cellular and animal models of FD.

Methods: PEG-CZNPs were synthesized using a non-hydrolytic sol-gel reaction method. HK-2 cells were transfected with α-galactosidase A (α-GLA) shRNA for permanent cellular model of FD. For in-vivo study 4-week-old male B6;129-Gla^{tm1Kul}/J mice were treated for 48 weeks with 10mg/kg of PEG-CZNPs twice per week via intraperitoneal injection. PCR, immunoblotting, immunoflouresce assay, electron microscopy analysis, ICP-MS, biochemical and histological analysis were done

Results: TFEB tanslocated to the nucleus by treatment with PEG-CZNPs. Autophagy flux was evaluated with chloroquine. Autophagy flux was enhanced by PEG-CZNPs treatment. To show whether TFEB plays the important role in autophagy flux, we transfected HK-2 cells with siTFEB. Autophagy flux significantly decreased after knockdown of TFEB with PEG-CZNPs treatment. We next assessed upper signaling pathway of TFEB by PEG-CZNPs. TFEB dephosphorylation was independent of both mTOR and ERK but GSK3ß signaling pathway showed massive impact on TFEB dephosphoryation by PEG-CZNPs. PEG-CZNPs decrease intracellular globotriaosyceramide (Gb3) accumulation and decreased the levels of Collagen type IV, αSMA and MMP9 expression in cellular model of FD. Gb3 levels were significantly reduced in the kidney tissues and the levels of Fibronectin, Collagen type 4 and αSMA was decreased by PEG-CZNPs in animal model of FD.

Conclusions: These results suggested PEG-CZNPs promote autophagy flux through GSK3ß -TFEB signaling pathways, showed the beneficial effect on renal fibrosis in cellular and animal models of FD. It thus provided a new insights of the potential therapeutics on FD.