Shaping Tomorrow's Nephrology: Insight-Driven Kidney Care
KSN SEOUL, KOREA 2026
The 46th Annual Meeting of the Korean Society of Nephrology
THE KOREAN SOCIETY OF NEPHROLOGY
Jun 11 (Thu) – 14 (Sun), 2026
COEX, Seoul, Korea

Abstract Type : Oral presentation
Abstract Submission No.: A-0311
Abstract Topic : Basic Research

Fabry Disease is Ameliorated by Long-Term PEG-Capped Ceria-Zirconia Nanoparticles via GSK3beta-TFEB-Mediated Restoration of Cholesterol Homeostasis

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Objectives : Fabry disease (FD), caused by α-galactosidase A (α-GLA) deficiency, leads to lysosomal accumulation of globotriaosylceramide (Gb3), impaired autophagy, and disrupted cholesterol metabolism. PEG-capped ceria–zirconia nanoparticles (PEG–CZNPs) have been reported to activate the AKT/GSK3β–TFEB pathway and enhance autophagy flux in FD models; however, their role in restoring cholesterol metabolism has not been defined. We aimed to investigate whether long-term administration of PEG–CZNPs restores cholesterol homeostasis.
Methods : Transcriptomic profiling was performed in α-GLA–deficient HK-2 cells, followed by validation using qRT-PCR, immunoblotting, and cholesterol efflux/uptake analyses. TFEB and GSK3β dependency was assessed using TFEB siRNA and a constitutively active GSK3β plasmid. Therapeutic efficacy was evaluated in α-GLA knockout mice administered PEG–CZNPs (10 mg/kg intraperitoneally, twice weekly from 4 weeks to 72 or 96 weeks of age), with analyses of renal function, Gb3 accumulation, cholesterol metabolism-related genes, and autophagy markers.
Results : Transcriptomic analyses revealed marked suppression of cholesterol metabolism–related pathways in α-GLA–deficient HK-2 cells, including downregulation of APOE, PLTP, and VDAC1. PEG–CZNPs restored expression of these genes, reduced intracellular cholesterol accumulation, enhanced cholesterol efflux, and decreased cholesterol uptake. These effects were abolished by TFEB knockdown or constitutively active GSK3β, confirming GSK3β–TFEB dependency. In vivo, long-term administration of PEG–CZNPs markedly reduced Gb3 accumulation, improved renal function, restored APOE and VDAC1 expression, enhanced TFEB nuclear localization, and reduced LC3B accumulation without detectable toxicity.
Conclusions : PEG–CZNPs correct α-GLA deficiency–induced cholesterol metabolic dysfunction by activating TFEB through GSK3β inhibition, thereby restoring cholesterol homeostasis and autophagy. These findings demonstrate that PEG–CZNPs represent a promising long-term nanotherapeutic strategy for FD.