Targeting membrane lipid peroxidation rescues podocyte dysfunction in cystinosis

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Background

Cystinosis is a rare, incurable, autosomal recessive storage disease caused by mutations in the CTNS gene and leading to lysosomal cystine accumulation in all cells of the body. While cystinosis is considered as a prototype of proximal tubular dysfunction, the disease also affects glomerular podocytes and presents with increased podocyte losses into urine and glomerular proteinuria at early disease stages. Cysteamine, the current standard of care treatment, decreases lysosomal cystine accumulation but does not reverse podocyte injury. Thus, other pathogenic mechanisms than mere cystine accumulation are involved in glomerular dysfunction in cystinosis.

Methods

Immortalized patient-derived cystinosis, healthy podocytes and CTNS-/- knockdown podocytes were used and the results were validated in our newly in-house developed fluorescent ctns-/- zebrafish larvae model (l-fabp:DBP-eGFP;CTNS). To understand the impaired podocyte functionality, static and dynamic permeability assay, metabolomics analysis (LC-MS), flow cytometry, RT-qPCR, western blot, chemical and dynamic roGFP2 redox-sensing fluorescent probes were used.

Results

Cystinosis podocytes present decreased adhesion, increased permeability and ferroptosis cell death caused by an accumulation of mitochondrial ROS-driven lipid membrane peroxidation. Moreover, they show fragmented mitochondrial network with impaired energy and TCA cycle metabolism and decreased superoxide scavenging SOD2 enzyme. Targeting mitochondrial ROS (with MitoTEMPO in combination with cysteamine) or lipid
peroxidation (with Liproxstatin-1 alone) improved podocytes dysfunction *in vitro* and rescues proteinuria *in vivo* in cystinosis zebrafish larvae.

Conclusions: mitochondrial dysfunction leading to increased ROS production and subsequent lipid peroxidation drive podocyte detachment and ferroptosis and play a key role in podocyte injury in cystinosis. Targeting these mechanisms represents a new therapeutic prospective for nephropathic cystinosis.