Hum Mol Genet. 2013 Dec 6. [Epub ahead of print]

Dedifferentiation and Aberrations of the Endolysosomal Compartment Characterize the Early Stage of Nephropathic Cystinosis.

Raggi C, Luciani A, Nevo N, Antignac C, Terryn S, Devuyst O.

Author information

- Division of Nephrology, Univeristé catholique de Louvain, Brussels, Belgium.

Abstract

Nephropathic cystinosis, a lysosomal storage disease caused by mutations in the CTNS gene encoding the lysosomal cystine transporter cystinosin, is characterized by generalized proximal tubule dysfunction that progresses, if untreated, to end-stage renal disease. The pathogenesis of defective proximal tubule cellular transport in nephropathic cystinosis remains unclear. We characterized a recently generated line of C57BL/6 Ctns mice and analyzed endocytic uptake, lysosome function, and dedifferentiation and proliferation markers using primary cultures of proximal tubule epithelial cells derived from $Ctns^{-/-}$ and $Ctns^{+/+}$ littermates. Metabolic studies revealed that $Ctns^{-/-}$ mice show a progressive proximal tubule dysfunction characterized by low-molecular-weight proteinuria, glucosuria and phosphaturia, before structural damage and in absence of renal failure. These changes are related to decreased expression of the multi-ligand receptors megalin and cubilin and to increased dedifferentiation (ZONAB transcription factor) and proliferation (PCNA and Cyclin D1) rates. Studies on proximal tubule cells derived from $Ctns^{-/-}$ kidneys confirmed cystine overload, with accumulation of enlarged, dysfunctional lysosomes and reduced expression of endocytic receptors reflected by decreased uptake of specific ligands. These changes were related to a loss of integrity of tight junctions with a nuclear translocation of ZONAB and increased proliferation, as observed in $Ctns^{-/-}$ kidneys. These data reveal that the absence of cystinosin in proximal tubule cells triggers aberrations of the endolysosomal compartment, transport defects and an abnormal transcription program in the early stage of nephropathic cystinosis. Insights into the early manifestations of cystinosis may offer new targets for intervention, before irreversible renal damage.

PMID: 24319100 [PubMed - as supplied by publisher]