Nature Reviews Nephrology **10**, 544 (2014); published online 12 August 2014; doi:10.1038/nrneph.2014.142

CYSTIC KIDNEY DISEASE

Intracellular clusterin implicated in nephropathic cystinosis

Increasing evidence suggests that cystine accumulation alone might not be responsible or sufficient for metabolic alterations in nephropathic cystinosis. Now, Minnie Sarwal and colleagues report a role of intracellular clusterin in the pathogenesis of this disease.

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The researchers previously used high-throughput complementary DNA microarrays to compare the gene expression patterns of individuals with and without nephropathic cystinosis. As further analysis of these data identified significant enrichment of clusterin in cell death pathways, they have now focused on the role of this protein in cellular injury.

Sarwal and colleagues found that cystinotic renal proximal tubular epithelial cells overexpressed the pro-apoptotic intracellular form of clusterin and produced significantly lower levels of the cytoprotective secretory form of the protein than did normal cells. In kidney biopsy samples from patients with cystinosis, clusterin was primarily expressed in the proximal tubules; this staining pattern differed from that seen in healthy kidney tissue (little or no expression) and in kidney tissue from patients with other renal diseases (low-level diffuse staining).

"To investigate the potential link between clusterin overexpression, autophagy and apoptosis, we applied double immunofluorescence staining specific for clusterin and markers of autophagy (LC3 II and p62) or apoptosis (AIF and cleaved caspase-3)," says Sarwal. Clusterin expression overlapped substantially with that of these markers in renal proximal tubular epithelial cells from patients with nephropathic cystinosis. Such overlap was not observed in normal renal proximal tubular epithelial cells.

Finally, the researchers showed that silencing clusterin gene expression using short-interfering RNA increased viability and attenuated apoptosis in renal proximal tubular epithelial cells from patients with nephropathic cystinosis, but not in disease-free controls. "Elevated intracellular clusterin is toxic to already stressed cystinosis kidney cells, which are laden with cystine crystals and contain aggregates of autophagic vesicles," explains Sarwal.

"Our findings highlight a new role for intracellular clusterin in cystinosis," she concludes. "Our ultimate goal is to establish clusterin as a novel therapeutic target—eventually leading to new drug development or the repositioning of an existing drug to treat renal insufficiency and circumvent the need for renal transplantation in patients with nephropathic cystinosis."

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Original article Sansanwal, P. & Sarwal, M. M. Inhibition of intracellular clusterin attenuates cell death in nephropathic cystinosis. *J. Am. Soc. Nephrol.* doi:10.1681/ASN.2013060577