Advancing the Understanding of the Renal Fanconi Syndrome in Cystinosis

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The autosomal recessive disorder, cystinosis is accounted as the most common hereditary cause of renal Fanconi syndrome. The Fanconi syndrome characterized by a defect in proximal tubular reabsorption of amino acids, glucose, phosphate, uric acid, bicarbonates, and excessive urine loss. This symptom starts in infancy before cystine build up in organs and cysteamine treatment does not prevent renal Fanconi Syndrome. This strongly suggests that cystinosin has other function than cystine transporter in the kidney. Currently, we aim to determine the underlying molecular mechanism behind the development of renal Fanconi syndrome.

Here we report a novel interacting partner of cystinosin which belongs to the sodium/hydrogen exchanger (NHE) family, the sodium/hydrogen exchanger isoform 3 (NHE3). NHE3 is the major absorptive sodium transporter expressed in the apical (brush border) membrane of the proximal tubule of the kidney, the endosomal compartment and in the gastrointestinal epithelial cells.

A study involving the integral membrane proteins interactome in yeast (*Saccharomyces cerevisiae*) found a positive interaction between the only ortholog of *CTNS* in yeast **(ERS1)** and the only sodium/hydrogen (Na/H) exchanger in yeast **(NHX1).** This was also confirmed by our collaborator Dr. Jean-Claude Farre (UCSD), thus laying a solid foundation for our study. We also confirmed interaction and colocalization of cystinosin and NHE3 in mammalian cells. This interaction seems to play an active role in normal kidney function. We also showed that NHE3 was mislocalized in CTNS-deficient proximal tubular cells (PTCs). Therefore, our hypothesis is that cystinosin might play an active role in the subcellular localization and/or function of NHE3 in the PTCs, and in its absence, NHE3 homeostasis is dysregulated leading to the renal Fanconi syndrome in cystinosis.

We expect our study to provide answers regarding the role of cystinosin beyond its lysosomal cystine transporter function and why defects in this protein first impacts the kidney function. This work could lead to the discovery of new drug targets to treat the renal Fanconi syndrome in cystinosis.