Layman's Explanation: Altered protein kinase signalling as a cause of reduced adhesion and increased motility of renal epithelial cells in cystinosis

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Short report

Cystinosis is a genetic disease manifesting early in life (≈ 6-12 months) with progressive kidney disease resulting in renal failure early during childhood if not treated. In cystinosis the metabolism of the amino acid cystine is defective leading to its accumulation in the kidney and other organs. This cystine accumulation results in cellular damage, but the direct mechanisms beyond this phenomenon are largely unknown. Some harmful cellular events in cystinosis might not be directly related to cystine accumulation and are the subject of our research project. In our previous work we demonstrated that both cellular motility and adhesion were altered in cultured human podocytes derived from cystinosis patients.

We tried to explore the mechanisms beyond this cellular loss. In cystinotic podocytes we found an increased expression of activated or phosphorylated Akt kinases compared to control cells. This could explain, at least partially, the abnormal phenotype.

We studied the adhesion of different podocyte cell lines (both cystinotic and control) with the use of different adhesion surfaces such as collagen IV, laminin and fibronectin. Interestingly different cell lines preferred different surfaces for adhesion as the control podocytes adhered more to collagen while cystinotic podocytes preferred fibrionectin. We also analyzed the protein structure of different adhesion molecules through the proteomic analysis by mass spectrometry in both control and cystinotic podocytes, but these experiments are still ongoing.

We further plan to knock-down the CTNS gene in control podocyte cells (the knocking-down protocol is currently being established in our lab), and compare the gene expression profile of many genes involved in motility and adhesion in the cells before and after knocking down of the CTNS. And we are going to perform the proteomic analysis for the knocked-down cells in comparison with the controls. Then we are going to combine the genetic expression data with the proteomic data to explain the mechanism behind the altered motility and adhesion in the cystinotic epithelial cells.

We also established a new zebrafish animal model expressing many of the cystinosis manifestations including cystine accumulation and the early tubular and glomerular dysfunction [Elmonem et al, Scientific Reports, 2017]. We believe that this zebrafish model can be suitable for the study of the disease pathology, and can be also suitable for the detailed study of toxicity and efficiency of new potential drugs that can improve the disease therapy.