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Commentary

Fat Burning Problem in Cystic Kidneys: an Emerging Common Mechanism of Chronic Kidney Disease

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Autosomal dominant polycystic kidney disease (ADPKD) is one of the most common genetic disorders, occurring in approximately 1 in every 1000 live births (Wilson, 2004). About 50% of people who inherit the mutation will develop chronic kidney disease (CKD), characterized by the development of multiple large cysts in both kidneys followed by functional decline and end-stage renal disease. While the genetic mutations in polycystin 1 and polycystin 2 (*PKD1* and *PKD2*, respectively) (Rangan et al., 2015) were identified more than 30 years ago, the mechanism of disease development remains largely unknown (Reeders et al., 1985). Menezes et al. took an unbiased systems-biology approach to study *Pkd1* gene function and report their results in the current issue of EBioMedicine (Menezes et al., 2016).

The authors performed genome wide transcript profiling on mice with conditional deletion of *Pkd1*, a model of ADPKD. They noted that disease severity was much milder in female mice when compared to their male counterparts. Metabolic genes represented the largest differentially expressed gene cluster, which correlated with disease development. Specifically, they identified differences in expression levels of several important regulators of lipid metabolism, which they probed further with unbiased metabolomics and lipidomics studies. Lipidomics studies highlighted several significant differences between control and *Pkd1* knockout animals, including significantly lower diacylglycerol levels in mutant kidneys. Diacylglycerol is a byproduct of triglyceride metabolism. This prompted the authors to take a closer look at fatty acid oxidation. Cell culture studies showed that renal epithelial cells lacking *Pkd1* have a cell autonomous defect in fatty acid oxidation, as these cells not oxidize palmitate as efficiently as control cells. Even though previous studies indicated changes in glucose metabolism in ADPKD, specifically an increased reliance on glucose as an energy source (Rowe et al., 2013), Menezes et al. were unable to detect changes in the glycolytic capacities of ADPKD cells.

Throughout the body, specific tissues and cells have evolved individualized metabolic patterns. Tubular epithelial cells in the kidney require large amounts of energy, mostly to reabsorb filtered electrolytes and to eliminate potential toxins. This process has a high energy demand. Although constituting only 0.5% of body mass, kidneys consume 10% of the oxygen. To fuel this high energy consumption, tubule epithelial cells preferentially take up and oxidize fatty acids as their energy source and have a very high mitochondrial density (Meyer et al., 1997). Gene expression studies performed on microdissected tubule samples obtained from patients with (diabetic and hypertensive) chronic kidney disease (CKD) compared to healthy subjects highlighted that fatty acid metabolism is altered in human CKD samples (Kang et al., 2015). In addition, cell culture studies indicate that CKD tubule cells are unable to switch to alternative fuel source such as glucose to efficiently generate energy. When lacking in energy, tubule cells are left dedifferentiated, unable to perform energy-demanding transport functions. Results of the present study indicate that the defect in lipid metabolism is not specific for a CKD type and most likely can be seen in all forms CKD.

Future studies should aim to understand molecular alterations observed in the metabolism of CKD kidneys. Are these problems caused by a defect in a single step in fatty acid oxidation, or multiple steps are altered due to transcriptional regulatory defect? Current observations hint that the defect is upstream at the transcriptional regulation of rate limiting enzymes. Changes can be observed in critical transcription factors such as PPARA and PPARGC1a. It is likely that these upstream transcription factors balance energy generation with energy consuming cell type-specific function. This is likely achieved by transcription factor cooperativity. Future research therefore should focus on understanding the transcriptional regulatory network that controls the energetics of renal tubule cells.

To what extent do these metabolic defects contribute to the progression of ADPKD and other forms of CKD? While, Menezes et al. did not directly address the role of lipid metabolism in PKD kidneys, they did show that even a small (2%) increase in fat in animals' diets worsened disease severity, potentially indicating that lipids play a role in ADPKD progression. The contribution of a lipid metabolism defect to other forms of CKD has already been established. Transgenic expression of PPARA or its co-activator PPARGC1A ameliorates fibrosis development induced by toxins (e.g., folic acid) or urethral obstruction, but effects

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of these manipulations have not been tested in ADPKD models. Pharmacological activation of PPARA or its upstream regulator AMPK has shown to effectively reduce scarring in mouse fibrosis models. Metformin, a widely used antidiabetic drug and pharmacological activator of AMPK, has already been shown to reduce cystogenesis in ADPKD animal model (Takiar et al., 2011), indicating commonalities in the pathway. On the other hand, these results would also indicate that activation of PPARA with fenofibrate might actually be beneficial for subjects with ADPKD. While the use of fenofibrate in the clinic is limited because it raises serum creatinine level. Clinical studies (FIELD and ACCORD) indicate that it can significantly reduce albuminuria and other intermediate CKD markers in patients with diabetes-associated CKD.

As with many new discoveries, we have more questions than answers. For example, how does mutation in membrane proteins, such as PKD1 or PKD2, result in a defect in fatty acid oxidation? What is the role of serum lipids in CKD development? Can we influence CKD development in patients by changing the fat composition of their diet?

In summary, the work by Menezes provides an excellent illustration of how unbiased high-throughput methods are able to highlight potentially targetable mechanisms in disease pathogenesis. In kidney diseases, integrated data analysis, including transcript and metabolite profiling indicate that proper fatty acid oxidation plays a critical role in CKD development.

Conflicts of interest

The Susztak lab received research support from Boehringer Ingelheim and Biogen for projects that are not related to this work.

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