Compelling “metabolomic” biomarkers may signal PKD pathogenesis

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AN ELEGANT STUDY (7) is contained in an issue of the American Journal of Physiology-Renal Physiology that discovers potential urinary biomarkers that are relatively common metabolites from various metabolic pathways. While this author is not an expert in metabolism, the fact that purine metabolism was shown to be upregulated in the study evoked a “déjà vu all over again” response from this author to the findings. While performing academic research on extracellular purinergic signaling and PKD, our laboratory performed experiments on primary human noncystic and cystic kidney epithelial cells and showed that both basal and stimulated ATP secretion (release, efflux) were potentiated in cystic cell cultures grown on plastic or on permeable filter supports versus companion noncystic cell controls (9). We also showed high (nanomolar to micromolar) amounts of ATP in flash-frozen cyst fluid tapped from human ADPKD cysts in a subset of the samples to complement and show in vivo relevance for our work (9). We concluded that this could be due to an upregulation in secretory ATP transport and/or exocytosis of ATP-filled granules. Alternatively, we conceded that this observation might also be reflective of enhanced metabolism, possibly derived from enhanced proliferation of cystic cells. We also made the argument then that trapped ATP and its metabolites (adenosine) would be detrimental to the progression of PKD in two ways. First, ATP and adenosine are known mitogens or comitogens for many cell types derived from different tissues. Second, ATP and adenosine stimulate salt and fluid secretion across epithelia via different signaling mechanisms. We also hypothesized that ATP’s metabolites (especially adenosine) might also accumulate in high amounts and also be detrimental for the same reasons. However, we had no way to measure adenosine easily at the time and not enough sample with which to do HPLC measurements.

In follow-on papers from our laboratory (3, 5, 6) as well as in studies on liver and bile duct by Doctor and coworkers (1) and in studies in Madin-Darby canine kidney cell cysts by Turner and coworkers (8), it has been clearly demonstrated that ATP secretion mechanisms, ATP receptors (P2X receptor channels and P2Y G protein-coupled receptors), and ion and water channels stimulated by autocrine and paracrine extracellular nucleotide and nucleoside signaling are present in human and mouse cystic epithelial cells. Normally, this signaling would take place either in the tubuluar fluid or interstitium, but it would either be carried downstream to other nephron segments or it would diffuse away with the interstitium (3). Extracellular ATP is also quickly metabolized into ADP, 5’ AMP, and adenosine by ecto-ATPases, ecto-ADPases, and ecto-nucleotidases. Robson, Friedman, Kishore and colleagues, as well as other have mapped many of these enzymes elegantly along the nephron (2, 4). However, upon cyst encapsulation before cyst expansion, extracellular ATP and adenosine signaling would continue to occur. As a consequence, it might then represent a detrimental signaling system when the PKD cysts fully encapsulate and autocrine and paracrine signaling becomes trapped in the cyst lumen, drawing solutes and water into the cyst lumen causing osmotic expansion of cyst volume (3).

The PKD mouse metabolomics paper (7) makes a strong argument that extracellular purinergic signaling is augmented in PKD, likely due to enhanced metabolism. Indeed, the galactose metabolic pathway is also affected, yielding allantoic acid as another candidate biomarker (7). Other metabolites derived from purine and galactose metabolism were also upregulated along with a handful of other candi-

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Fig. 1. Remodeling of renal tissue leading to autosomal dominant polycystic kidney disease (ADPKD) and its possible impact of appearance of metabolites in the final urine of PKD patients. A loss of differentiation and an enhanced rate of proliferation lead to change in renal tissue architecture leading to ADPKD. This phenotype likely increases cellular metabolism, leading to the appearance of metabolites such as adenosine and allantoic acid in the final urine of diseased mice. It is important to emphasize that this enhanced growth is not neoplastic in nature. In human ADPKD, this remodeling occurs all along the nephron. In PKD, encapsulated cysts lose contact with the nephron and surrounding renal tissue. These cysts are usually fluid-filled. Enhanced appearance of metabolites in later stages of the disease in mice or humans may become muddled when a larger number of PKD cysts have encapsulated fully and the metabolites of interest become increasingly trapped in cyst fluids.

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date biomarkers. Whether a “hyperproliferative state,” a hallmark of PKD pathogenesis, is driving enhanced metabolism or whether augmented metabolism is driving higher rates of cell growth observed with cystic kidney cells is now a central question worth investigating. Importantly for clinical diagnosis, Taylor et al. (7) identify a handful of potential biomarkers of metabolism that would be relatively easy to detect via simple biochemical test. Hopefully, a subset of these will also be predictive in the human condition, paving the way for simple diagnostic testing of a urine sample that might yield an earlier and better diagnosis than ultrasound or other methods that screen for emergence of cysts visually on the surface of the kidney.

A simple cartoon (Fig. 1) is included that illustrates the findings of this paper. It also proposes an explanation as to why the upregulated biomarkers may be less evident in older mice or subjects with advanced disease. Taylor et al. (7) contend that this is due to a higher and more variable body weight within the older cystic mice as well as other considerations. While this is certainly plausible, could this also be explained by a higher degree of cyst encapsulation from the normal nephron, an effect that would cause these biomarkers to be trapped more than appear in the final urine? This alternative explanation should be taken into account because PKD pathogenesis has at least two phases. The first phase is tissue remodeling and hyperproliferation of cystic cells within normal renal parenchyma. As the first phase continues, a second phase emerges where fully encapsulated cysts begin to expand in size, volume and number. Both phases contribute to the overall enlargement of the kidney tissue over time.

In closing, Taylor et al. (7) have brought “metabolomics” into the same realm with the active and ongoing genomic and proteomic approaches. Together, they are leading advances in understanding PKD pathogenesis while also pursuing an end goal of defining and identifying genetic, biochemical, and metabolic biomarkers that are predictive of either or both forms of PKD as well as related cystic kidney diseases. With any disease, an earlier diagnosis, especially one that involves a noninvasive measurement, allows clinicians to intervene earlier and often, be more preventative and likely more effective in treating PKD patients.

REFERENCES