Environmental hit on a genetic basis in polycystic kidney disease

Shixuan Wang and Zheng Dong *

Department of Cellular Biology and Anatomy, Medical College of Georgia, Augusta University and Charlie Norwood VA Medical Center, Augusta, GA 30912

* Correspondence:
Zheng Dong, PhD

Department of Cellular Biology and Anatomy, Medical College of Georgia, Augusta University and Charlie Norwood VA Medical Center, Augusta, GA 30912. Email: zdong@augusta.edu
For many years, efforts have been made to determine the pathogenetic mechanism of autosomal dominant polycystic kidney disease (ADPKD). The most remarkable breakthrough is the discovery of \textit{PKD1}, mutations of which is associated with 85\% of ADPKD cases. \textit{PKD1} is a large gene spanning 46 exons to code a 4,302 amino-acid protein called Polycystin 1 (PC1). Haploinsufficiency or dominant negative mechanism of \textit{PKD1} was earlier proposed as the cause of ADPKD. Later, the functional loss of the wild-type allele in some heterozygous cells of renal cysts was found. Thus, a two-hit model of cystogenesis was proposed. Recent years have witnessed several notable advances in this research field. One of the landmark discoveries in the early 2000s is the subcellular localization of PC1 on the primary cilia of renal tubular cells for sensing fluid flow (3), at which PC1 forms a protein complex with Polycystin 2 (PC2). More recently, kidney injury has drawn much attention as ischemia/reperfusion injury (IRI) or toxic kidney injury was found to promote the development of PKD (1, 4, 7). Thus, kidney injury may be an accelerant, an epistatic modulator, or a third hit for cystogenesis.

In a recent issue of the \textit{American Journal of Physiology Renal Physiology}, Kurbegovic and Trudel (2) studied the effect of IRI on cystogenesis with \textit{Pkd1} transgenic mice. Surprisingly, they found 100\% penetrance and similar onset and severity of cystogenesis in transgenic and non-transgenic mice after IRI. They also found increased and sustained PC1 and PC2 expression in both IRI transgenic and non-transgenic kidneys, accompanied by the changes in a few of PKD and acute kidney injury (AKI)-shared signaling pathways. Interestingly, they observed that IRI \textit{per se} causes PKD irrespective of \textit{Pkd1} transgene, which is not fully in agreement with the previous publications (1, 4, 7). As we know, kidney injury severity and recovery after IRI are determined by many factors, such as mouse strain, age, gender, body temperature during surgery, anesthesia, and injury time (9), among which the ischemia time is critical. Mildly injured kidneys
may completely recover. However, if ischemia lasts long, animal death may occur soon after AKI, or if the animal survives, acute injury may gradually progress into chronic pathologies. In the study of Kurbegovic and Trudel, IRI caused widespread damage to the kidney. Thus, the discrepancy between this study and the others may be due to the sensitivity of IRI, which led to unresolved tubular degeneration as well as proliferation months later resulting in cystogenesis. Under this condition, the effect of Pkd1 transgene was masked because PC1 was markedly induced in wild-type mice to a level apparently sufficient to trigger cystogenesis. Regardless, the study of Kurbegovic and Trudel informs us that ischemic injury may cause cystogenesis in the kidney even without the first hit at genetic level, indicating the importance of environmental factors in the pathogenesis of PKD (6). Of note, in addition to renal IRI, there are many other kinds of micro-environmental insults that may do just the same.

The observation of PC1 and PC2 induction in renal IRI is consistent with previous report (5). However, the role of increased PC proteins in cystogenesis remains unclear. Increased apoptosis in ADPKD patients and Pkd1 knockout mice suggests that PC1 may be a protective molecule. But, overexpression of Pkd1 in mice leads to PKD as well (8) indicating that increment of PC1 dosage is not beneficial. Indeed, some cysts of ADPKD patients express high level of PC1. It is possible that high expression of PC1 and/or PC2 contributes to ADPKD, but the increase of PC1 and PC2 may also be a compensatory response in ADPKD. Such possibilities are difficult to distinguish in animals. Thus, it would be valuable to establish a relevant cell model to analyze how different dosages of PC1 and PC2 regulate cystogenesis, and how these proteins and cystogenesis are affected by environmental factors.

The study by Kurbegovic and Trudel also touched upon a few of key signaling pathways shared by PKD and renal IRI. Induction of Hif1α after IRI is not surprising, but high Hif1α
expression detected in late stage of human ADPKD and PKD animal model is intriguing. They further found dysregulation of mTOR signaling in IRI mice and suggested that this signaling pathway may play a role in kidney repair/progression. Wnt/β-catenin pathway is involved in the regulation of c-Myc. Both full-length c-Myc and cytoplasmic cleaved form Myc-nick are increased markedly after IRI. These signaling analyses suggest that PKD and AKI hold many similarities. Together, these findings support the idea that ischemic stress contributes to ADPKD. Then, does it exclude the role of Pkd1/ Pkd2 or PC1/PC2? Obviously not. Years of research has already established these genes as the genetic basis of ADPKD. The recent studies including the one by Kurbegovic and Trudel, however, have shed lights on the significance of environmental factors in the pathogenesis of ADPKD.

GRANTS
This study was supported by grants from the National Institutes of Health (DK058831, DK087843) and Department of Veterans Administration of USA.

DISCLOSURES
No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS
Author contributions: S.W. and Z.D. drafted manuscript; S.W. and Z.D. edited and revised manuscript; S.W. and Z.D. approved final version of manuscript.
REFERENCES


