A unique feature of the developing postnatal kidney is that tubular diameter remains relatively constant even as it elongates severalfold. After acute kidney injury, tubular epithelial cells also divide and restore tubule morphology without affecting luminal diameter. Strict control of luminal diameter is critical for maintaining normal renal function. An increase in luminal diameter causes tubular dilation and subsequent formation of cysts and chronic kidney disease, which are hallmarks of autosomal dominant polycystic kidney disease.

Autosomal dominant polycystic kidney disease (PKD) arises as a result of mutations of the PKD1 or PKD2 genes, which encode proteins polycystin 1 (PC1) and polycystin 2 (PC2), respectively.1 Besides other locations in the cell, PC1 and PC2 are found in the primary cilium, a hair-like structure present on the surface of most cells in the body.2 Several murine studies showed that inducing the loss of primary cilia or Pkd1 in the postnatal kidney, specifically during tubule elongation or tubule repair after injury, results in the formation of cysts.3–5 These cysts derive from tubules indicating that PC1 and primary cilia are critical for the maintenance of normal tubule diameter; so how do primary cilia and PC1 regulate the tubule diameter? Rapidly accumulating evidence suggests that primary cilia, PC1, and other cystic disease genes regulate the tubule diameter through the planar cell polarity (PCP) pathway.

PCP refers to the spatial organization of cells along a tissue plane that is orthogonal or perpendicular to the apical-basal axis.9,10 PCP is best described in fruit fly, Drosophila melanogaster, where the hairs on the wing always point distally toward the wing tip. Mutations in proteins referred to as the “core PCP” proteins produce distortions of the wing hair pattern and disrupt PCP. The PCP pathway is also called the noncanonical Wnt signaling pathway because Wnt pathway proteins Frizzled and Dishevelled function as the core PCP proteins. PCP regulates oriented cell division (OCD), convergent extension (CE), and other morphogenic processes. The core PCP proteins are evolutionarily conserved in mammals, and recent evidence indicated that PCP is observed in various mammalian organs such as the inner ear, skin, and kidney.

Two PCP-regulated processes, CE and OCD, modulate tubule lumen diameter.6,7 CE is a process by which rearrangement of cells within a tissue makes the tissue longer and narrower. In the embryonic kidney, CE movements of the tubular epithelial cells are thought to increase the tubule length while reducing its luminal diameter until the proper diameter is established.7 In the postnatal kidney, luminal diameter is maintained by OCD. Dividing tubular epithelial cells in the developing or regenerating postnatal kidney are almost always oriented parallel to the longitudinal axis of the renal tubule3,6,7,11; hence, OCD ensures that renal tubules grow only along the longitudinal axis, causing an increase in length of the tubule without affecting diameter.

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### Balancing the Wnts in Polycystic Kidney Disease

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At least two lines of evidence suggest that aberrant PCP results in tubular dilation and subsequent cyst formation. First, several orthologous and nonorthologous rodent mod-
els of PKD display defective CE or randomization of angle of cell division, both signs of aberrant PCP signaling.\(^3,6,7\) Second, loss of Fat4, a core PCP protein, results in aberrant PCP and the formation of kidney cysts in mice.\(^8\)

In this issue of *JASN*, Luyten et al.\(^12\) provide more support for the notion that aberrant PCP underlies the pathogenesis of kidney cyst formation. Previously, the authors showed that loss of *Pkd1* in developing or regenerating postnatal kidney results in formation of cysts. Here, they show that aberrant PCP, evidenced by the randomization of angle of cell division, precedes cyst formation in these mice. These results are in stark contrast to a recent study also published in *JASN*,\(^13\) which found that the randomization of angle of cell division does not precede cyst formation in mice with kidney-specific inactivation of *Pkd1* during embryogenesis.

Differences between the two mouse models, which include the timing of inactivation of *Pkd1*, rate of cyst formation, and age at which angle of cell division was measured, may be responsible for the dissimilar results. To explore the molecular mechanism, the authors studied the status of Fzd3, a frizzled receptor that regulates PCP signaling, and its downstream effector, Cdc42, a Rho family GTPase. In this regard, the authors described several novel results. They found that Fzd3 is expressed in the primary cilium and that in kidneys from *Pkd1* mutant mice and humans with autosomal dominant PKD, Fzd3 and Cdc42 were overexpressed. Furthermore, the authors found that PC1 and Fzd3 exhibit opposite effects. Inducing expression of PC1 in cells causes a reduction in Cdc42 expression, whereas Fzd3 had opposite effects. In addition, overexpression of Fzd3 and Cdc42 slows the rate at which cells migrate in a wound-healing assay. Reexpression of PC1 in these cells normalizes the rate of cell migration.

On the basis of these results, the conclusion is that the loss of *Pkd1* results in aberrant PCP due to overexpression of Fzd3 and Cdc42; however, the answer may not be that straightforward. First, Cdc42 is a multifaceted protein involved in signaling pathways that regulate diverse processes such as apical-basal polarity, adherens junction formation, vesicle trafficking, and cell-cycle progression; therefore, overexpression of Cdc42 may produce changes in these other processes besides abnormalities in PCP. Second, the loss of OCD was observed in the precystic kidneys, whereas Fzd3 overexpression was observed only at later stages in the cystic kidneys. This suggests that aberrant PCP signaling occurs as a Fzd3-independent mechanism. Finally, Fzd3 homodimerization and Cdc42 activate canonical Wnt (β-catenin–dependent) signaling. The authors found that besides aberrant PCP, canonical Wnt signaling was inappropriately activated in *Pkd1* mutant mice. This latter finding raises the possibility that overexpression of Fzd3 or Cdc42 represents a mechanism for abnormal canonical Wnt signaling in the *Pkd1* mutant kidneys.

The study by Luyten et al.\(^12\) generates several unanswered questions. Similar to the wound-healing assay, does the loss of PC1 in *vivo* also result in defective cell migration, especially in the kidney? Does PC1 regulate other PCP-dependent processes such as CE? In support of the role of PC1 in CE, *Pkd1* null mice display neural tube defects, a classic phenotype observed as a result of aberrant CE. As suggested by the authors, to clarify the role of Fzd3 and Cdc42 in PCP signaling, it would be pertinent to determine whether these proteins are also overexpressed in neural tube epithelia. Another interesting finding presented here is the concomitant deregulation of both canonical Wnt and PCP signaling pathways in *Pkd1* mutant mice. Similar results have been found in kidney-specific *Kif3a* mutant mice that lack primary cilia in the renal tubules.\(^14\)

The mechanism by which primary cilia modulate canonical Wnt and PCP signaling may involve inversin, a ciliary protein mutated in cystic kidney disease called nephronophthisis.\(^15,16\) Inversin constrains canonical Wnt signaling and stimulates PCP signaling.\(^15\) It will be interesting to determine whether PC1 functions in a similar manner. A common theme already emerging from these studies is that proper balance between canonical Wnt and PCP signaling is essential to maintaining the normal tubule lumen diameter. Other obvious questions raised by these studies are as follows: (1) What is the function of Fzd3 in the primary cilium? (2) Is it possible to retard cyst growth in *Pkd1* mutants by modulating the expression of Fzd3 and Cdc42 in the kidney? (3) Does PC1 act in concert with PC2 to regulate these processes?

**ACKNOWLEDGMENTS**

I am supported by grants from the National Institutes of Health/National Institute of Diabetes and Digestive and Kidney Diseases (K08 DK084311-01) and UT Southwestern O’Brien Research Core Center (P30DK079328).

**DISCLOSURES**

None.

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Progress in Progression?

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Diabetic nephropathy is the major cause of ESRD in the United States.1 Unfortunately, only angiotensin-converting enzyme inhibitors or angiotensin type 1 receptor blockers are regis-

tered for slowing the progression of diabetic nephropathy—but they do not halt progression.2–5 Given that diabetic nephropathy costs the health care system close to $30 billion per year,6 one would hope to see a flurry of active clinical trials aimed at registering new therapies to slow progression. Instead, the sad truth is that only 31 interventional phase 2 or 3 trials are currently listed on ClinicalTrials.gov and most only study various angiotensin-converting enzyme inhibitor/angiotensin type 1 receptor blocker and renin inhibitor combinations. In striking contrast, there are 757 breast cancer and 989 lung cancer interventional survival trials and 175 interventional major adverse cardiac event outcomes trials in the same database.7

Numerous hurdles exist to closing this gap for diabetic nephropathy, including the identification of dynamic biomarkers that reflect not just the presence of disease but also the rate of loss of kidney function.8,9 Discovery of these biomarkers and novel therapies will require a deeper understanding of the pathophysiology of diabetic nephropathy. Because of limited access to diseased human kidney tissues, validated and clinically relevant animal models of diabetic nephropathy would significantly facilitate these efforts.

The laboratory mouse represents a unique experimental platform offering unprecedented genetic characterization and capability for genetic engineering.10–15 Characterization of diabetes and its associated renal phenotype in mice provides hope that the right mouse model will elucidate the pathophysiology of human diabetic nephropathy. The National Institutes of Health–sponsored Animal Models of Diabetic Complications Consortium (AMDCC) recently outlined three major phenotypes needed for a robust mouse model of diabetic nephropathy:6 More than 50% decline in GFR over the lifetime of the animal; >10-fold increase in albuminuria compared with controls for that strain at the same age and gender; and pathology in kidneys showing advanced mesangial matrix expansion with or without nodular sclerosis and mesangiolysis, any degree of arteriolar hyalinosis, glomerular basement membrane (GBM) thickening by >50% over baseline, and tubulointerstitial fibrosis.

Of these criteria, only decline in GFR translates to a clinical end point successfully used in trials to register a drug for diabetic nephropathy—that being a doubling of the serum creatinine. Reductions in proteinuria have yet to be accepted as a surrogate end point for registration by regulatory agencies,17 and it is not practical to run a phase 3 trial on the basis of pathology, because this would require serial kidney biopsies to monitor an unproven therapy. Unfortunately, no mouse model of diabetic nephropathy thus far exhibits a progressive halving of the GFR. In fact, few mouse models exhibit convincing histopathologic changes of diabetic nephropathy or progressively increasing albuminuria. These deficiencies have significantly impeded our ability to link changes in histopathology to biomarker discovery and limit confidence that preclinical efficacy in mice will translate into meaningful clinical effects in humans.