mTOR is out of control in polycystic kidney disease

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Autosomal-dominant polycystic kidney disease (ADPKD) is a common genetic disease caused by mutations in the PKD1 gene. This adult-onset disease results in the accumulation of destructive kidney cysts, leading to progressive loss of renal function and eventually to renal failure. A need for kidney transplantation and dialysis are common outcomes. There are currently no treatment options to prevent or delay the disease onset. Although the PKD1 gene was identified more than a decade ago, the development of treatment strategies has been hampered by a lack of understanding of the function of polycystin-1 (PC1), the protein encoded by the PKD1 gene (1, 2). Work by Shillingford et al. (3) in this issue of PNAS now identifies a new function of PC1, which immediately suggests a possibility for future treatment options.

PC1 is a very large integral membrane protein with a much smaller C-terminal cytoplasmic tail. Previous work had implicated this tail in numerous signaling events, but their relevance to ADPKD had remained largely unclear. Shillingford et al. (3) now report that the PC1 tail interacts with a very interesting player by the name of tuberin, the product of the TSC2 gene. Tuberin mutations lead to the complex disease tuberous sclerosis (TSC), which is ~10 times less common than ADPKD. Three earlier observations had already suggested that tuberin and PC1 could be functionally linked. First, in addition to benign tumors in multiple organs, TSC patients also exhibit kidney cysts. Second, the TSC2 gene is located only a handful of base pairs away from the PKD1 gene. A subset of patients has larger chromosomal deletions that affect both the TSC2 and the PKD1 genes at the same time. These patients suffer from very severe, early onset polycystic kidney disease. Third, previous results using tuberin null cells had suggested that tuberin may play a role in intracellular trafficking of PC1 (4). These observations led Shillingford et al. (3) to investigate the possibility that tuberin may interact with the PC1 tail. This possibility could indeed be shown by forced colocalization experiments in vivo and binding experiments in vitro. To elucidate functional consequences of this interaction, the authors capitalized on a recent wealth of information on the function of tuberin. Its main function appears to be to inactivate the Ser/Thr kinase mTOR (5, 6). mTOR, in turn, promotes translation via phosphorylation of two proteins, S6-kinase and 4E-BP1 (Fig. 1). mTOR activity has been linked to increased cell growth, proliferation, apoptosis, and changes in differentiation (7).

Reasoning that the interaction between PC1 and tuberin may have functional consequences for mTOR activity, Shillingford et al. (3) tested whether mTOR activity is altered in ADPKD or a PC1-inactivated mouse model. Indeed, in both cases cystic epithelial cells exhibited very high mTOR activity. Furthermore, forced colocalization experiments suggested that mTOR may also be part of the PC1–tuberin complex. These results suggest that PC1 normally suppresses mTOR activity and that defects in PC1 consequently lead to aberrant mTOR activation. A working model consistent with these findings is shown in Fig. 1.

Interestingly, the authors also found excessive mTOR activity in kidney cysts of mouse models with defects in proteins other than PC1. A host of proteins has recently emerged that, when mutated, results in renal cystic diseases in humans or animal models. Although the function of none of these proteins is clear, they all have something in common: they all localize to primary cilia of renal epithelial cells or to the basal bodies from which cilia emanate. This finding has led to the widely held view that loss of cilia function

Conflict of interest statement: No conflicts declared.
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leads to cyst formation in the kidney (8, 9). But what is the function of cilia in the kidney? These nonmotile organelles project from the apical plasma membrane of epithelial cells into the lumen of the renal tubules. After many decades of accusing primary cilia of being vestigial structures, at least one function has recently emerged when they were shown to act as mechanosensors of intraluminal fluid flow: bending of cilia results in the elevation of cytoplasmic calcium (10). PCI-null cells have been found to be defective in this flow response (11), which suggests that (i) PCI is required for mechanotransduction and (ii) loss of ciliary mechanotransduction somehow leads to the growth of renal cysts. The finding by Shillingford et al. (3) that mTOR is inappropriate activated not only in PCI-defective cysts but also in polycystic mouse models with defects in different proteins (namely, polaris and MAL) suggests that mTOR activation may be a common consequence of the loss of cilia function. If mTOR is indeed such a converging point, then it would be of great interest as a possible drug target for treatment of renal cystic diseases.

mTOR (for “mammalian target of rapamycin”) is a protein that is named after the drug that inhibits it. Rapamycin is a compound originally discovered in the 1970s in soil from Easter Island. It very specifically and effectively inhibits mTOR (12). Rapamycin is clinically approved as an immunosuppressant and is mostly used in kidney transplant patients. When Shillingford et al. (2) treated two different polycystic mouse models with rapamycin, the results were stunning. In a mild, late-onset mouse model, rapamycin treatment for 1 month not only stopped kidney growth but resulted in a regression of kidney size. This result was shown to be likely because of the induction of programmed cell death (apoptosis) specifically in cyst lining epithelial cells. In contrast, rapamycin seemed to have no effect in the kidneys of normal mice. Treatment of an aggressive, early onset mouse model with rapamycin for 2 weeks resulted in a dramatic reduction of kidney size and prevented the loss of kidney function. Because inhibition of mTOR alone had these dramatic beneficial effects, this result suggests that the inappropriate activation of mTOR is of central importance for the growth of renal cysts and further supports the idea that mTOR lies at a converging point of signaling pathways that lead to cyst formation.

Drugs that work well in animal models often fail to be effective in human trials. To obtain preliminary information on the possible effectiveness of rapamycin in human ADPKD patients, Shillingford et al. (3) made use of the facts that this drug is clinically approved to immunosuppress kidney transplant patients and that ADPKD patients frequently undergo kidney transplantation. Typically, ADPKD patients receive the transplant in addition to their remaining native kidneys. These patients therefore have three kidneys, two of which are polycystic. Some of these patients are being treated with rapamycin. In their retrospective study, Shillingford et al. (3) identified a group of such patients who also had computed tomography (CT) scans performed at the beginning of the treatment and ~2 years later. In this rapamycin group, the kidney volumes decreased by 25%, whereas there was no effect in a nonrapamycin control group. Although the patient numbers are probably too small for this result to be definite, the data are highly encouraging because they point in the right direction.

Overall, the functional link between mTOR and PC1 and the effects of rapamycin on animal models and patients suggest that rapamycin may be a promising drug with the potential to become the first available treatment for ADPKD patients. The fact that this drug is already clinically approved should greatly facilitate clinical trials.

Besides these exciting clinical implications, this work also raises many important basic science questions. Which other regulatory proteins (such as Rho and hamartin; see Fig. 1) are involved in the PC1–tuberin–mTOR complex? Is there a cilia connection? If so, is mTOR activity regulated by fluid flow and cilia bending? Very recent work by the same laboratory identified another novel pathway involving the PC1 tail (13). These results suggested that another function of PC1 is to sequester the transcription factor signal transducers and activators of transcription 6 (STAT6) in cilium under normal conditions. In the absence of fluid flow through the kidney, however, the tail of PC1 is cleaved by a protease and translocates together with STAT6 to the nucleus, where it activates gene expression (13). This novel cilial mechanotransduction pathway may be the long-sought-after mechanism of cilia function in the kidney, but how does it relate to the activation of mTOR? It will be exciting to find answers to these questions.