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See related article, "ZONAB Promotes Proliferation and Represses Differentiation of Proximal Tubule Epithelial Cells," on pages 478–488.

Of Mice and Men: Therapeutic mTOR Inhibition in Polycystic Kidney Disease

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Autosomal dominant polycystic kidney disease (ADPKD) is the most common monogenic kidney disease and accounts for approximately 5% of ESRD in developed countries. Focal development of renal cysts, which increase in number and size with age, leads to distortion of the normal kidney architecture and ultimately ESRD in a majority of patients by the fifth decade of life. Currently, clinical management of ADPKD is limited to nonspecific measures such as BP control, dialysis, and transplantation.

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Most cases of ADPKD are due to mutations of two genes: *PKD1* and *PKD2*. Positional cloning of *PKD1* in 1995 and *PKD2* in 1996 represented a major research landmark and provided researchers essential genomic reagents for elucidating the molecular pathogenesis of ADPKD.[1,2] In the past 15 years, we have witnessed important advances in our fundamental understanding of ADPKD. For example, we have learned that polycystin-1 and -2, the proteins encoded by *PKD1* and *PKD2*, respectively, are components of a novel multifunctional signaling pathway that regulates growth, differentiation, and maintenance of three-dimensional spatial orientation of tubular epithelial cells[3]; that complete loss or significant reduction of polycystin levels beyond a critical threshold within tubular epithelial cells triggers clonal formation of individual cysts[4,5]; that the polycystin-1/2 complex at the primary cilium serves as a mechanosensor of urine flow to modulate calcium influx and intracellular signaling[3,6]; and that perturbation of multiple signaling pathways modifies growth of renal cysts.[7,8]

The next decade holds the exciting possibility that some of these novel insights may be translated into mechanism-based drug treatments that target renal cyst growth and thereby delay or prevent ESRD. Indeed, a recent review highlighted at least six classes of drugs with distinct mechanisms to modulate intracellular calcium, cAMP, CFTR chloride channels, MAPK-ERK, mTOR signaling, or cell cycle that may have therapeutic potential for human ADPKD.[8]

The mammalian target of rapamycin (mTOR) is a serine/threonine kinase that functions as a sensor and integrator of nutrient availability and growth factor stimulation to regulate cell size, proliferation, and survival.[9] Inhibition of mTOR signaling was proposed recently as a promising approach for treatment of ADPKD. The first clue that mTOR may be involved in the pathogenesis of ADPKD is provided by the observation of patients with a rare syndrome in which genomic deletion of *PKD1* and the adjacent gene, *TSC2*, results in unusually severe renal cystic disease and ESRD by the second decade of life. *TSC2* mutations cause tuberous sclerosis, another renal cystic disease, and tuberin, the protein encoded by *TSC2*, is an upstream regulator of mTOR. Thus, increased renal disease severity seen in this syndrome compared with ADPKD or tuberous sclerosis alone suggests a synergistic interaction of polycystin-1 and tuberin pathways, possibly through mTOR.[10] In a later study, Shillingford *et al.*[11] showed that polycystin-1 indeed interacts with tuberin *in vitro*, that mTOR activity is aberrantly activated in cystic epithelia of patients with ADPKD, and that experimental mTOR inhibition significantly ameliorates renal cystic disease in orpk-rescue and bpk mouse models. The efficacy of rapamycin was also demonstrated in the Han rat and folliculin mouse models of PKD,[12] and two small, retrospective, case-control studies showed that rapamycin treatment associates with regression of native polycystic kidney or liver volume in renal transplant patients with ADPKD.[11,13] Collectively, these data suggest a potential therapeutic role of mTOR inhibition in ADPKD; however, none of the experimental studies that demonstrate the efficacy of rapamy-

cin used an orthologous model of human ADPKD. Nevertheless, two randomized clinical trials have been launched to test the efficacy of mTOR inhibition in ADPKD.[8]

In this issue of *JASN*, Shillingford *et al.*[12] answer the much anticipated question, "Does mTOR inhibition work in an orthologous model of human ADPKD?" Using the $Pkd1^{cond/cond}$:Nes^{cre} conditional null mice, they showed that nestin Cre-mediated deletion of *Pkd1* alleles results in aberrant mTOR activation in cystic epithelia, moderate cystic disease by 4 weeks of age, and severe cystic disease and renal failure by 7 weeks of age. Experimental mTOR inhibition starting at 4 weeks of age results in dramatic regression of renal cyst size and preservation of renal function. Mechanistically, these therapeutic effects are related to decreased proliferation and increased apoptosis of cystic epithelia and decreased interstitial fibrosis. Moreover, although the rapamycin dosage (5 mg/kg) used is much higher than that used in organ transplants, the steady-state drug levels are comparable to those seen in transplant recipients. Taken together, these data demonstrate both efficacy and feasibility of this experimental approach and provides a strong justification for ongoing human clinical trials.

Despite these promising results, it is unclear whether mTOR inhibition will work in human ADPKD. As acknowledged by Shillingford *et al.*,[12] there is no perfect mouse model that completely replicates human ADPKD in which biallelic inactivation of *PKD1* or *PKD2* through germline and somatic mutations within individual epithelial cells is thought to be a common albeit nonexclusive mechanism for cyst formation.[3–5,14,15] More recent studies showed the response of tubular epithelia to acquired somatic loss of *Pkd1* is determined by the developmental state of the kidneys: Conditional inactivation of *Pkd1* in mice before postnatal day 13 results in severely cystic kidneys within 3 to 6 weeks, whereas inactivation at day 14 or later results in focal cysts after 3 to 5 months and severe cystic disease only by 1 year of age.[14,15] These dramatically different responses to *Pkd1* inactivation between the very young and older mice suggest that different pathways may be altered between the two groups. To date, most published mouse models used for testing therapies for ADPKD (including this study, which induced early *Pkd1* loss in a mosaic pattern) result in a rapid course, compressing into several months the cystic disease that develops over several decades in patients.[14] Given the marked differences in the kinetics of cyst expansion,[14,15] it is unclear whether any drug treatment proven effective in the early-onset models will be equally effective for the slowly progressive human ADPKD. In addition, serious long-term adverse effects of mTOR inhibition, particularly cancer, may not be predictable by animal studies. Thus, the efficacy and tolerability of mTOR inhibition in ADPKD can be answered ultimately only by well-conducted randomized, controlled trials of patients. With cautious optimism, the PKD community looks forward to the completion of the human studies.

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