Drugs of the Future 2006, 31(7): 611-615

CCC: 0377-8282/2006
DOI: 10.1358/dof.2006.031.07.995040



# Autosomal dominant polycystic kidney disease

***Elisa Ferrer, Jordi Bozzo***
*Prous Science, P.O. Box 540, 08080 Barcelona, Spain*

**CONTENTS**



**Abstract**

Autosomal dominant polycystic kidney disease (ADPKD) is the most common form of polycystic kidney diseases, which are genetic disorders characterized by the abnormal growth of numerous cysts in the kidneys. ADPKD is one of the leading causes of end-stage renal failure. It results from mutations in two genes, *PKD1* and *PKD2*, with *PKD1* mutations accounting for more than 80% of cases. Currently, there is no cure for ADPKD and traditional treatments have been supportive, aimed at ameliorating associated symptoms and complications. However, the advances in understanding the pathophysiology of this disease will lead to more targeted therapeutic strategies to prevent cyst formation.

## Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is one of the most common inherited disorders, occurring in approximately 1/1,000 individuals in the general population. It is characterized by the development of fluid-filled cysts in any segment along the nephron that progressively increase in size leading to tubular malformation and renal fibrosis, which ultimately results in renal failure. Typically, kidney enlargement is due to the presence of hundreds to thousands of cysts of different sizes distributed throughout the renal cortex and medulla. In most cases, disease manifestations may be delayed until the fourth or fifth decade of life. Renal complications such as hematuria, polyuria or flank pain are common and related to kidney structural abnormalities. Secondary urinary tract infections are also frequent in cystic kidneys. Hypertension is the most common associated complication due to increased secretion of renin in tubules and cysts of ADPKD kidneys and often precedes the onset of renal insufficiency. By the age of 60, approximately 50% of patients experience end-stage renal disease, requiring dialysis or transplantation. Extrarenal manifestations can also occur in ADPKD and include the presence of cysts in different organs, being especially frequent in liver, but without seriously affecting hepatic function (1, 2).

## Molecular pathophysiology

ADPKD is a genetic disease caused by mutations in two genes, *PKD1* and *PKD2*, which encode for the proteins polycystin-1 (PC1) and polycystin-2 (PC2), respectively. Most ADPKD cases (> 80%) are due to mutations of the *PKD1* gene and are associated with an earlier onset and faster disease progression than the *PKD2* phenotype. A subset of patients with no associated mutations in *PKD1* or *PKD2* but presenting the typical clinical picture of ADPKD has been described, suggesting it might be a third form of the disease, although the putative gene (*PKD3*) has not been identified. A recent study reported that *PKD1* overexpression is sufficient to develop a polycystic kidney disease phenotype, indicating that any *PKD1* dysfunction (gain or loss of function) can lead to cystogenesis (3).

ADPKD has been widely studied during the last decade, having shed new light on polycystin structure and function. PC1 and PC2 are highly conserved, ubiquitous transmembrane proteins that, in the kidney, are located in epithelial cells of renal tubules, in particular in the primary cilia at the luminal side of the tubules, as well as in other areas of the renal cell epithelium. PC1 is a large protein with a long extracellular *N*-terminal region, 11 transmembrane domains and a short intracellular *C*-terminal tail. The extracellular *N*-terminal domain contains motifs involved in protein-protein and protein-carbohydrate interaction. Fibronectin, collagen and laminin bind to PC1 through these domains. The 200-amino-acid intracellular tail has several phosphorylation sites involved in activation of intracellular signaling cascades that will lead to gene transcription. PC2 is structurally related to the transient receptor potential (TRP) channel family and is known to function as a nonselective cation channel permeable to $Ca^{2+}$. Although the cellular localization of PC2 is still controversial, having been identified in the plasma membrane as well as in the endoplasmic reticulum, PC1 and PC2 are known to form heteromeric complexes through a coiled region in the intracellular domain of PC1 that binds to the last 97 amino acids in PC2.

Polycystin complexes have been localized to anchoring junctions in the renal cell epithelium contributing to cell-extracellular matrix interactions (focal adhesions), and also to junctions between neighboring epithelial cells (adherens junctions). Interaction with the adherens junction protein E-cadherin, critical to morphogenesis and development, has suggested a role for polycystin complexes in maintaining correct epithelial cell function. In fact, disruption of the E-cadherin-polycystin interaction reported in ADPKD renal epithelial cells may contribute to altered cell differentiation and morphology, resulting in abnormal cyst formation and growth (4).

As mentioned earlier, PC1 and PC2 also co-localize in the primary cilium of renal epithelial cells. The primary cilium is a long nonmotile tubular structure located in the apical surface of epithelial cells in renal tubules. Its function was unknown for a long time. However, recent studies proposed a role for the primary cilium as a mechanoreceptor that may sense changes in apical fluid flow and may be able to transduce them into an intracellular $Ca^{2+}$ signaling response (5). This model involves the participation of PC1 as a mechanical sensor of ciliary bending induced by luminal fluid flow. Bending of the cilium would cause a conformational change in PC1 that would in turn activate the PC2-associated $Ca^{2+}$ channel. $Ca^{2+}$ influx would subsequently stimulate intracellular ryanodine-sensitive stores to release $Ca^{2+}$ to the cytosol, thus increasing the intracellular $Ca^{2+}$ concentration ($[Ca^{2+}]_i$) through $Ca^{2+}$-induced $Ca^{2+}$ release. The resulting increase in cytosolic $Ca^{2+}$ would then trigger intracellular signaling pathways leading to normal kidney development. This hypothesis shares similar features to blood vessel remodeling in response to shear stress in the vascular system, where structural adaptation of vessels is necessary to maintain a constant blood flow. In contrast, in mice lacking PC1, changes in fluid flow do not result in an increased $[Ca^{2+}]_i$, thus blocking all downstream $Ca^{2+}$-dependent signaling (5). Therefore, the inability to respond to changes in fluid flow as a consequence of abnormal primary cilia function due to PC1 mutations would prevent normal cell differentiation and kidney morphogenesis, contributing to cyst formation.

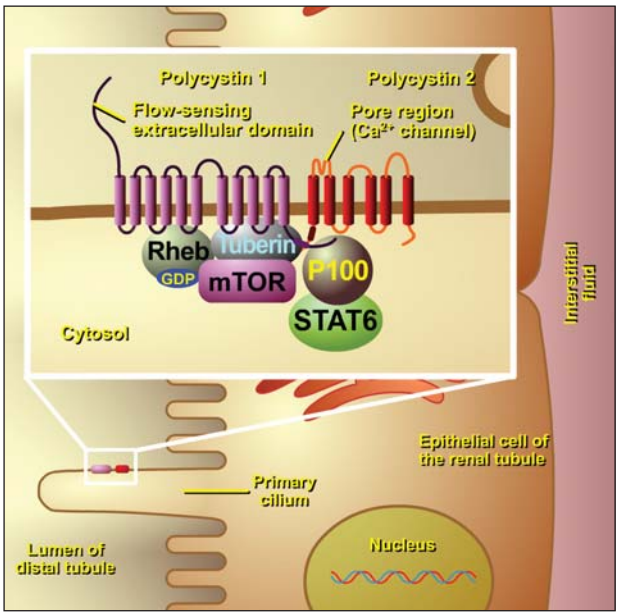



Fig. 1. Urine flows across the luminal surface of the epithelial cells that form the renal tubules. The flow-sensing domain resides in the primary cilium and involves the proteins polycystin 1 and 2 (PC1 and PC2), which form a complex in the plasma membrane. The large extracellular domain of PC1 is sensitive to mechanical stress, which can induce a conformational change that activates PC2, resulting in calcium entry. Calcium influx acts as an intracellular second messenger to transduce the mechanical signal into the cell. Under normal urine flow conditions, STAT6 is assembled in a complex with PC1 and P100. The PC1 tail has also been described to be assembled in a complex with mTOR, tuberin and the small G-protein Rheb. PC1/tuberin complexes negatively regulate mTOR activation.

**Therapeutic targets and potential treatments (Table I)**

Further research has provided insights on other mechanotransduction pathways that appear to be important in ADPKD. In situations of normal fluid flow, PC1 has been reported to form a complex with the transcription factor STAT6 at the primary cilia and prevent the transcription of genes that may be involved in cyst growth. However, when luminal urine flow is impaired, as occurs in ADPKD, PC1 would undergo cleavage, abandon the cilia membrane and translocate to the nucleus together with STAT6, where it would promote transcription of genes associated with cyst growth and proliferation (6) (Figs. 1 and 2).

Cyclic AMP has also been described as a regulator of cyst formation and proliferation of ADPKD cells *in vitro*. Normal kidney cells, in contrast, do not appear to exhibit these cAMP-dependent effects (7, 8). cAMP may stimulate cell proliferation via sequential activation of the Ras/B-Raf/MEK/ERK pathway, which has not been found to be activated in normal human renal epithelial cells. In contrast, normal cells maintain the activity of the phosphatidylinositol 3-kinase (PI3K)/Akt signaling pathway, which negatively regulates the activation of B-Raf. Reduced intracellular $Ca^{2+}$ levels in ADPKD appear to be responsible for differences in the response to cAMP, as it has been shown that elevation in $[Ca^{2+}]_i$ can rescue a normal phenotype in ADPKD cells (8). Sorafenib (Bay-43-9006) has recently been approved for advanced renal cancer, but could also be potentially useful in ADPKD. This Raf kinase inhibitor has been shown to decrease the proliferation of human ADPKD cells *in vitro* and also significantly reduced cyst growth by blocking cAMP- and EGF-dependent activation of B-Raf (9).

Treatments for ADPKD have been classically supportive, oriented to reducing symptoms and preventing associated complications. End-stage kidney disease usually requires dialysis or renal transplantation, both associated with excellent outcomes and no recurrence of ADPKD in transplanted kidneys. However, newer

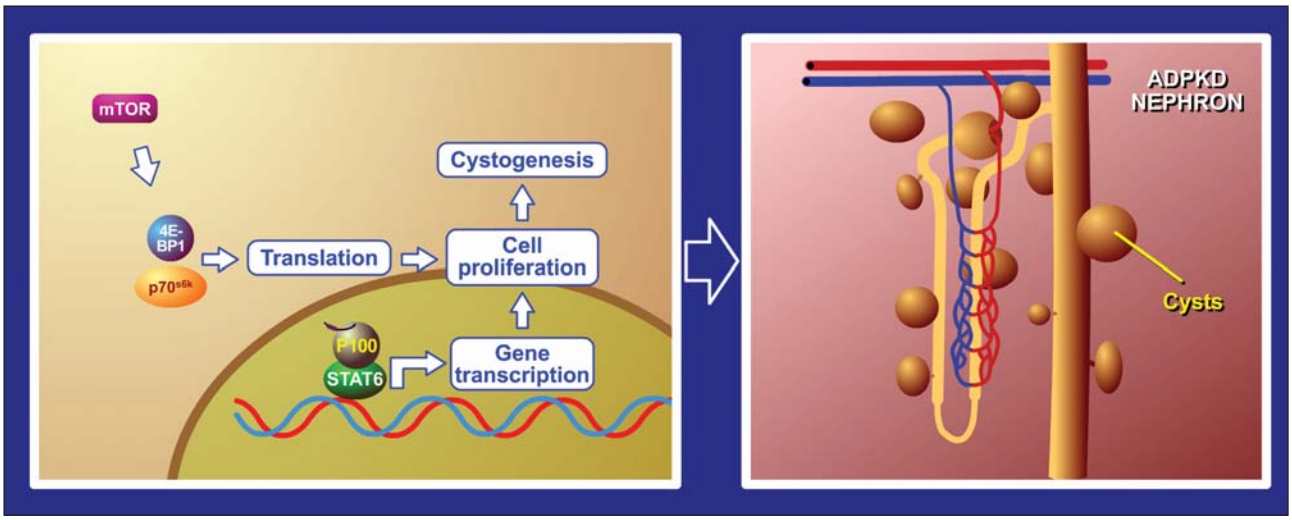
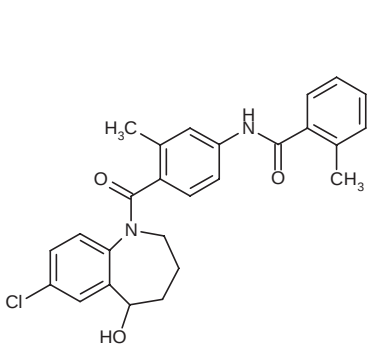


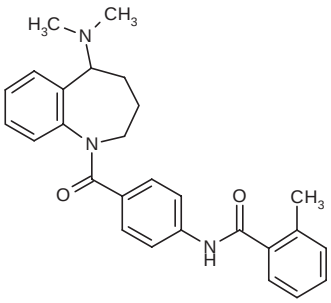

Fig. 2. Cessation of urine flow or abnormal PC1 function will trigger cleavage of the cytoplasmic tail of PC1 and STAT6 tyrosine phosphorylation. The PC1 tail/STAT6/P100 complex translocates to the nucleus and activates gene expression. Also, if PC1 is defective or absent, the complex mTOR/tuberin/Rheb does not form and mTOR is activated. Activated mTOR promotes mRNA translation via phosphorylation of p70s6k and 4E-BP1 proteins. As a result, epithelial cells proliferate and cysts develop. In ADPKD, cystic outpushings arise in every tubule segment and rapidly close off from the nephron of origin.

*Table I: Drugs under active development for ADPKD (from Prous Science Integrity®).*

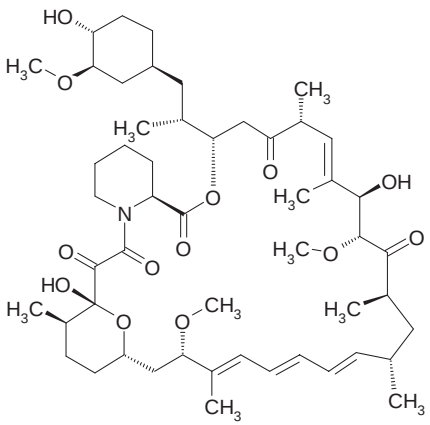
| Drug name | Source | Mechanism of action | Phase |
|---|---|---|---|
| 1. Tolvaptan | Otsuka | Vasopressin $V_2$ receptor antagonist | III |
| 2. Mozavaptan | Otsuka | Vasopressin $V_2$ receptor antagonist | Preclinical |
| 3. Sirolimus | The Cleveland Clinic | mTOR inhibitor | I/II |
| 4. Telmisartan | Boehringer Ingelheim | Angiotensin $AT_1$ receptor antagonist | II/III |
| 5. Lisinopril | Merck & Co. | Angiotensin I-converting enzyme inhibitor | II/III |



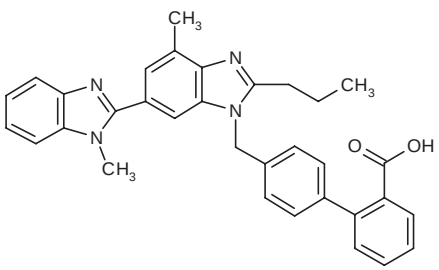
(**1**)



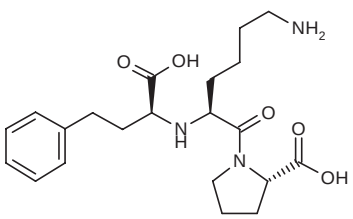
(**2**)



(**3**)



(**4**)



(**5**)

treatment options are being targeted to decrease cyst formation, mainly by means of inhibiting cAMP-dependent renal cystogenesis. Vasopressin $V_2$ receptor (VPV2R) antagonists have been reported to reduce renal cAMP and inhibit cyst development in a rat model of PKD (10, 11). Vasopressin mediates water reabsorption in the collecting duct through aquaporin-2 water channels, a process involving the activation of adenylyl cyclase and the formation of cAMP. Vasopressin $V_2$ receptors are selectively expressed in the principal cells of the collecting duct and endothelial cells, which makes VPV2R antagonists very attractive drug candidates to treat ADPKD. The VPV2R antagonist tolvaptan, developed by Otsuka Maryland Research Institute, was recently granted FDA fast track designation for the treatment of ADPKD since to date there is no effective therapy for the disease (12).

Other therapeutic approaches have targeted the mammalian target of rapamycin (mTOR), a protein kinase that controls cell growth and proliferation via the synthesis of new proteins. Initially, the mTOR inhibitor sirolimus (rapamycin), which is approved as an immunosuppressant and primarily used in kidney transplantation, was successfully tested in a rat model of ADPKD, where it clearly decreased cyst volume and prevented the loss of renal function (13, 14), although the exact mechanism of action is not known. Most recently, work by Shillingford *et al*. provided new evidence of the importance of the mTOR signaling pathway in the pathophysiology of ADPKD and as a potential therapeutic target (15). In this study, the mTOR pathway was found to be abnormally upregulated in cyst lining renal epithelial cells in human ADPKD and also in PC1-defective mouse models. Rapamycin was able to prevent cyst formation, decrease kidney size and improve kidney function, confirming its potential use in the clinical setting. Additionally, this work presented evidence to explain the regulation of mTOR by PC1. These authors demonstrated the presence of a membrane complex formed by PC1 and the protein tuberin. Tuberin is the product of *TSC2*, a tumor suppressor gene, which if mutated leads to the formation of benign tumors in multiple locations and renal cysts. Functional PC1 appears to be dependent on tuberin, since in the absence of tuberin PC1 does not translocate to the membrane (16). Furthermore, tuberin is known to inhibit mTOR activity under physiological conditions (17). In the model proposed by Shillingford and colleagues, in ADPKD the PC1/tuberin complex that downregulates mTOR activity may not be functional, leading to aberrant mTOR activation, which has an essential role in protein translation, cell growth and proliferation. Rapamycin will be tested in a phase I/II clinical trial for the treatment of ADPKD (18).

As mentioned above, hypertension is one of the most frequent complications of ADPKD and has been ascribed to an upregulation of the renin-angiotensin system (RAS) in renal cysts. In fact, the components of the RAS have been identified in cells isolated from renal cysts (19). The resultant increased angiotensin II production caused by overactivation of the RAS has been proposed to contribute to the development of hypertension. Therefore, inhibition of the RAS could slow the progression of cystic disease. This hypothesis will be assessed in two clinical trials using the antihypertensive drugs telmisartan and lisinopril in patients at different stages of ADPKD (20).

**Acknowledgements**

The authors thank Dr. Aleix Cases for his comments on the manuscript.

**References**

1. Al Bhalal, L., Akhtar, M. *Molecular basis of autosomal dominant polycystic kidney disease*. Adv Anat Pathol 2005, 12: 126-33.

2. Wilson, P.D. *Polycystic kidney disease*. New Engl J Med 2004, 350: 151-64.

3. Thivierge, C., Kurbegovic, A., Couillard, M., Guillaume, R., Cote, O., Trudel, M. *Overexpression of PKD1 causes polycystic kidney disease*. Mol Cell Biol 2006, 26: 1538-48.

4. Roitbak, T., Ward, C.J., Harris, P.C., Bacallao, R., Ness, S.A., Wandinger-Ness, A. *A polycystin-1 multiprotein complex is disrupted in polycystic kidney disease cells*. Mol Biol Cell 2004, 15: 1334-46.

5. Nauli, S.M., Alenghat, F.J., Luo, Y. et al. *Polycystins 1 and 2 mediate mechanosensation in the primary cilium of kidney cells*. Nat Genet 2003, 33: 129-37.

6. Low, S.H., Vasanth, S., Larson, C.H. et al. *Polycystin-1, STAT6, and P100 function in a pathway that transduces ciliary mechanosensation and is activated in polycystic kidney disease*. Dev Cell 2006, 10: 57-69.

7. Hanaoka, K., Guggino, W.B. *cAMP regulates cell proliferation and cyst formation in autosomal polycystic kidney disease cells*. J Am Soc Nephrol 2000, 11: 1179-87.

8. Yamaguchi, T., Hempson, S.J., Reif, G.A., Hedge, A.M., Wallace, D.P. *Calcium restores a normal proliferation phenotype in human polycystic kidney disease epithelial cells*. J Am Soc Nephrol 2006, 17: 178-87.

9. Yamaguchi, T., Grantham, J.J., Wallace, D.P. *BAY 43-9006, a novel Raf kinase inhibitor, blocks cAMP- and EGF-dependent ERK activation and the proliferation of ADPKD epithelial cells*. 38th Ann Meet Exposit Am Soc Nephrol (ASN): Renal Week 2005, Abst SA-PO125.

10. Gattone, V.H., Wang, X., Harris, P.C., Torres, V.E. *Inhibition of renal cystic disease development and progression by a vasopressin $V_2$ receptor antagonist*. Nat Med 2003, 9: 1323-6.

11. Torres, V.E., Wang, X., Qian, Q., Somlo, S., Harris, P.C., Gattone, V.H. *Effective treatment of an orthologous model of autosomal dominant polycystic kidney disease*. Nat Med 2004, 10: 363-4.

12. *Fast track status for tolvaptan in autosomal dominant polycystic kidney disease*. DailyDrugNews.com, February 27, 2006.

13. Tao, Y., Kim, J., Schrier, R.W., Edelstein, C.L. *Rapamycin markedly slows disease progression in a rat model of polycystic kidney disease*. J Am Soc Nephrol 2005, 16: 46-51.

14. Wahl, P.R., Serra, A.L., Le Hir, M., Molle, K.D., Hall, M.N., Wuthrich, R.P. *Inhibition of mTOR with sirolimus slows disease progression in Han:SPRD rats with autosomal dominant polycystic kidney disease (ADPKD)*. Nephrol Dial Transplant 2006, 21: 598-604.

15. Shillingfod, J.M., Murcia, N.S., Larson, C.H. et al. *The mTOR pathway is regulated by polycystin-1, and its inhibition reverses renal cystogenesis in polycystic kidney disease*. Proc Natl Acad Sci USA 2006, 103: 5466-71.

16. Kleymenova, E., Ibraghimov-Beskrovnaya, O., Kugoh, H. et al. *Tuberin-dependent membrane localization of polycystin-1: A functional link between polycystic kidney disease and the TSC2 tumor suppressor gene*. Mol Cell 2001, 7: 823-32.

17. Jozwiak, J., Jozwiak, S., Grzela, T., Lazarczyk, M. *Positive and negative regulation of TSC2 activity and its effects on downstream effectors of the mTOR pathway*. Neuromol Med 2005, 7: 287-96.

18. *Pilot study of rapamycin as treatment for autosomal dominant polycystic kidney disease (ADPKD) (NCT00286156)*. ClinicalTrials.gov Web Site 2006.

19. Loghman-Adham, M., Soto, C.E., Inagami, T., Cassis, L. *The intrarenal renin-angiotensin system in autosomal dominant polycystic kidney disease*. Am J Physiol Renal Physiol 2004, 287: F775-F788.

20. *HALT progression of polycystic kidney disease (HALT PKD) (NCT00283686)*. ClinicalTrials.gov Web Site 2006.

## Online links

Subscribers to Prous Science Integrity® can access an online animation (Figs. 1 and 2 in the printed version) to illustrate the pathophysiology of ADPKD.