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REVIEW

Treatment of autosomal dominant polycystic kidney disease (ADPKD): the new horizon for children with ADPKD

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Abstract Polycystic kidney disease (PKD) is the most common inherited renal disorder. Patients with PKD remain clinically asymptomatic for decades, while significant anatomic and physiologic systemic changes take place. Sequencing of the responsible genes and identification of their protein products have significantly expanded our understanding of the pathophysiology of PKD. The molecular basis for cystogenesis is being unraveled, leading to new targets for therapy and giving hope to millions of people suffering from PKD. This has direct implications for children with PKD with regard to screening for the disease and identification of high-risk individuals. In this article we provide a review of the clinical manifestations in children with autosomal dominant polycystic kidney disease (ADPKD), the genetic and molecular basis for the disease, and a concise review of potential therapies being evaluated.

Keywords Autosomal dominant polycystic kidney disease · PKD1 · PKD2 · Pediatric · Pathophysiology · Vasopressin receptor antagonists · cAMP · Somatostatin analogues

Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited renal disorder, affecting 1 in 800 live births in the United States of America. All races are equally affected, and ADPKD is responsible for 5% of the population with end-stage renal disease (ESRD). Although the genetic defect is present from conception, affected children are often oligo-symptomatic. Until now, there has been little incentive for pediatricians to diagnose asymptomatic children at risk for ADPKD, given the paucity of disease-specific therapies available. Such therapies are being investigated now and may become available in the near future, making an early diagnosis of ADPKD important to optimize interventions that change the progression of this disease. Pediatricians should, however, remain vigilant about following these at-risk children closely, so that they can implement interventions as early as possible when disease manifestations such as hypertension arise.

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Clinical manifestations

ADPKD is characterized by massive enlargement of the kidneys, due to gradual cyst development and growth that replace normal renal parenchyma. ADPKD is, however, not limited to the kidneys but involves multiple organ systems, including the liver, cerebral vasculature, connective tissue, and gastrointestinal system. Congenital abnormalities occur with increasing frequency in ADPKD and involve those temporally related during development. Cardiac, gastrointestinal and renal defects are the most common and include patent foramen ovale, horseshoe and agenic kidneys [1, 2]. The incidence of renal and extra-renal manifestations of ADPKD in adults and children is shown in Table 1.

Inguinal hernias occur in up to 10% of children with ADPKD and often offer the first clue that an at-risk child is affected. Liver, pancreatic epididymal and splenic cysts are common extra-renal manifestation of ADPKD in adults,

Table 1 The incidence of renal and extra-renal manifestations of ADPKD in adults and children

Manifestation	ADPKD in adults	ADPKD in children
Hematuria (micro- and macro-)	35–50% [68]	10% [68]
Concentrating defects	100% [7]	60% [65]
Proteinuria	18% [12]	14% [12]
Microalbuminuria	25% [12]	30% [12]
Nephrolithiasis	20% [66]	Unknown
Flank/abdominal pain	60% [11]	10% [11]
Hepatic cysts revealed by MRI	83% [5]	55% by age 25 years [5]
Colonic diverticula	82% [67]	Unknown
Cerebral aneurysms	5–7% [14]	Rare
Prolapse of the mitral valve	26% [9]	12% [9]
Hypertension prior to loss of renal function	60% [27]	22% [7]
Hyperlipidemia	Unknown	54% [10]

MRI Magnetic resonance imaging

with a prevalence of 70%, 16%, 18%, and 6.7%, respectively [3, 4]. Their frequency has not been systematically studied in children; however, individual cases have been reported. Liver cystic disease is the most common extra-renal feature in ADPKD, and, recently, magnetic resonance studies in young patients with ADPKD age 15–46 years demonstrated an 83% prevalence of liver cystic disease, with 55% demonstrating liver cysts prior to age 25 years [5]. Therefore, liver cystic disease may not be uncommon in children with ADPKD. Liver cysts are usually benign and do not affect hepatic function. Rare cases of congenital hepatic fibrosis have been described in children with ADPKD. In those cases, portal hypertension and hypersplenism precede renal manifestations and often dominate the clinical picture [6].

Studies of children with ADPKD reveal that hypertension is the earliest and most prevalent systemic feature of ADPKD, occurring in 5–44%, and correlates with the severity of structural renal disease, where those with increased renal volumes have increased systolic and diastolic blood pressures [7]. In addition, abnormal circadian blood pressure rhythms are present in children with ADPKD [8]. Other cardiovascular abnormalities found in affected children include mitral valve prolapse (12% ADPKD vs 3% unaffected children), increased left ventricular mass (87.1 gm/m^2 ADPKD vs 76 gm/m^2 control subjects), and hyperlipidemia (defined as a fasting cholesterol or triglyceride level above the 95th percentile for age and gender), detected in 54% of children with the disease [9, 10].

Independent of the classical findings of renal cystic disease, other renal abnormalities are present in children with ADPKD. Flank or abdominal pain is a common complaint, and gross hematuria occurs in approximately 10% of children with ADPKD. These clinical manifestations are associated with the presence of larger kidneys [11].

Proteinuria is usually low grade and relatively uncommon in ADPKD; however, microalbuminuria and proteinuria are more common in children with ADPKD than in adults with ADPKD. Of children with ADPKD, 30% (vs 25% of adults) have microalbuminuria and 23% (vs 17% of adults) have proteinuria (> 300 mg/day). As in adults, proteinuria in children with ADPKD correlates with diastolic hypertension and more severe cystic disease [12, 13].

Cerebral aneurysms are the most feared complications of ADPKD but occur in relatively few individuals (5–8%) and tend to cluster in families. Aneurysms can lead to significant morbidity, and to death, at the time of rupture [14]. Though rare, ruptured cerebral aneurysms have been described in children with ADPKD [15]. Screening for intracranial aneurysms (ICAs) should be done at the age of 20 years in high-risk patients, and repeat imaging should be offered at 10-year intervals for patients with a family history of ruptured ICAs [16, 17].

Pathogenesis

Two genes are responsible for the vast majority of ADPKD cases: *PKD1*, located on chromosome 16 (16p13.3), and *PKD2*, located on chromosome 4 (4q22), account for 85% and 15% of cases, respectively. A small number of families with ADPKD do not demonstrate linkage to either PKD1 or PKD2, which suggests the potential presence of a yet unidentified PKD3 gene. Although phenotypically identical to those with the *PKD1* gene, patients with the *PKD2* gene have a better prognosis, with a median age at death and/or onset of end-stage renal disease (ESRD) of 69.1 years, vs 53 years for patients with the *PKD1* gene [18].

PKD1 is made up of 46 exons, and polycystin 1, the gene product of *PKD1*, is a 4,302 amino acid protein with 11 transmembrane domains. The NH_2 terminal of the protein is extracellular, while the COOH terminal is intracellular. The functions of many of its domains remain unknown; however, some extracellular motifs suggest that polycystin 1 has the ability to interact with surrounding matrix and cell membrane proteins. The intracellular domains have many sites for phosphorylation and are in-

volved in signal transduction. Polycystin 1 has been found at the cell–cell junctions, in focal adhesion complexes, and, most recently, in the primary cilium [19].

PKD2 is a gene of 15 exons that codes for polycystin 2, a 968 amino acid protein with six transmembrane domains. Both its N and C terminals are intracellular. Polycystin 2 shares homology with voltage-activated calcium (Ca^{2+}) channels and increases membrane permeability to Ca^{2+}. Polycystin 2 has been found in the endoplasmic reticulum, the basolateral cell membrane, and the primary cilium. Polycystin 1 and polycystin 2 co-localize in all human tissues and interact through their C terminals intracellularly [19].

Cystogenesis

Information is now becoming available about cystogenesis, allowing new therapies to emerge and giving hope to millions of people suffering from the disease. Despite the presence of an inherited mutated gene in every renal epithelial cell, cysts in ADPKD arise from only 5% of nephrons. This fact, as well as the large variability in the course of the disease among family members, has led to the proposal of the two-hit hypothesis, which suggests that an inherited germline mutation has to be followed by an acquired somatic mutation in the normal allele for a cyst to develop. Microdissection studies isolating cysts from human ADPKD renal specimens have confirmed the two-hit hypothesis, showing that epithelial cells lining the cysts are clonal in origin and have loss of heterozygosity [20, 21]. ADPKD, therefore, has an autosomal dominant pattern of inheritance but is a molecularly recessive disease. Modifier genes also play a role in cystogenesis. For example, combined tuberous sclerosis gene (*TSC 2*) and *PKD1* mutations (or the contiguous gene syndrome due to large deletions in both adjacent genes) lead to severe and early onset of PKD, suggesting a synergistic role of both protein products [19, 22, 23].

Cystogenesis is, therefore, a complex process involving genetic events but also environmental factors that could affect the rate of somatic mutations as well as cyst progression.

Cysts in ADPKD can arise from all segments of the nephron; they expand and ultimately detach from the parent tubule but continue to grow. Simplistically, cyst formation involves three steps: cell proliferation, abnormal cell matrix and cell–cell interactions, and fluid excretion. Research has provided scientific support for each of these steps, and the role of polycystin 1 and polycystin 2 in these processes is now emerging.

Normal renal epithelium has relatively slow rates of cell turnover and apoptosis compared with that of cystic epithelium. Using monoclonal antibodies to proliferating cell nuclear antigen (PCNA), a polypeptide characteristic of the S phase of mitosis, researchers found that renal epithelial cells from human polycystic kidney specimens have a high index of proliferation [24]. Importantly, non-cystic tubular cells also had a high index of proliferation, which suggested that cellular hyperplasia precedes cyst formation [24]. Cyclic AMP, normally an inhibitor of renal epithelial cell division, acts as a promoter of cellular proliferation in PKD. Using nephrectomy specimens from patients with ADPKD, Belibi et al. studied the effect of several stimulators of adenylate cyclase, including epinephrine, arginine, vasopressin, adenosine, prostaglandin E2 and parathyroid hormone (PTH), on cyst epithelial cells and found that cAMP production is upregulated, which, in turn, activates an extracellular-regulated protein kinase, leading to increased cell proliferation [25, 26]. Concomitantly, epidermal growth factor (EGF) stimulates cell proliferation by activating extracellular signal-regulated protein kinase (ERK) through a tyrosine kinase pathway. Evidence supporting the role of EGF in cystogenesis includes its high concentration in cystic fluid, the upregulation of the EGF receptor (EGFR) in cystic epithelia, and its abnormal luminal location, allowing a sustained cycle of proliferation [27]. In parallel with this dysregulated proliferation, polycystic kidneys show evidence of increased apoptosis, which may lead to death of normal renal tissue, promoting progressive loss of function and allowing the expansion of existing cysts [28].

Mutant epithelial cells exhibit abnormal interactions with the extracellular matrix, including increased adherence to collagen type I and type IV [27]. Polycystin 1 is has been found in desmosomes. In ADPKD cells, polycystin 1 and desomosomal proteins move from their normal intercellular junction locations to the cytoplasmic space. In parallel, E cadherin is down-regulated and replaced by N cadherin at the cell surface. Mutated polycystin 1, therefore, clearly inhibits desmosomal junction formation and leads to abnormal cell–cell interactions [29]. Finally, cystic cells have disturbed polarity. which leads to an aberrant insertion of different channels, transporters and receptors [27]. Taken together, these abnormal cell–cell and cell–matrix interactions allow ADPKD epithelia to detach from their surroundings to form cysts.

Fluid secretion is a critical component of cystogenesis, allowing the expansion of cysts after they detach from their parent nephron. The accumulation of cyst fluid rich in Cl^- and Na^+ relies on the active luminal excretion of Cl^-, primarily through the cystic fibrosis transmembrane conductor regulator (CFTR). This creates an electronegative luminal environment that favors the passive exit of Na^+ into the urinary space. Increased intracellular cAMP levels lead to a rise in Cl^- passage through the CFTR, hence promoting fluid excretion [30, 31].

Despite these major advances in our understanding of the molecular basis of cyst formation, the direct roles of

polycystin 1 and polycystin 2 remained unclear until the two proteins were found in the primary cilium and the role of the cilium was elucidated. The primary cilium is a solitary, immotile, structure found on the apical surface of every epithelial cell that projects into the tubular lumen [19]. It acts as a chemomechano-sensor, allowing a flow stimulus to be converted to a chemical response. The flow of fluid into the tubular lumen bends the cilium. This mechanical stimulus is detected by the extracellular portion of polycystin 1, which, in turn, stimulates polycystin 2, allowing the influx of calcium across the cell membrane. This is followed by calcium-induced calcium release from the endoplasmic reticulum. The significant rise in intracellular Ca^{2+} levels activates, in turn, a signaling cascade involved in different cellular functions [32]. Cells with mutant polycystin 1 or 2 have no ciliary-dependent calcium influx. Using mouse —1 cortical collecting duct cells that have PKD features, Yamaguchi et al. showed that low intracellular calcium levels turn cAMP from a growth inhibitor to a growth stimulator of renal epithelial cells through activation of the B-Raf/ERK pathway [33, 34].

Diagnosis of ADPKD

Increased awareness of ADPKD has led to earlier diagnosis of the disease, with the average age at diagnosis being 27 years in those born between 1950 and 1974 vs 39 in those born before 1950. Knowledge of the Mendelian dominant transmission of the disease has allowed family history to become a common screening tool, prompting diagnosis [35]. Specific targeted therapeutic interventions may be more likely to have an impact on ADPKD if started early; therefore, it is likely that the screening of at-risk children will increase in the near future.

Renal ultrasound remains the diagnostic method of choice. Based on the Ravine criteria for patients with the *PKD1* gene, a screening ultrasound that reveals at least two renal cysts (bilateral or unilateral) in an at-risk individual younger than 30 years of age is diagnostic of the disease [36]. A more recent study of patients with the *PKD2* gene found similar results, with ultrasound being 100% reliable in excluding the disease only beyond the age of 30 years [37]. In a study assessing the utility of ultrasonography in the diagnosis of ADPKD in children, Gabow et al. found that the sensitivity of ultrasound is 77% and the specificity is 98% in at-risk children. In that study the presence of a single cyst was considered diagnostic. Sensitivity, but not specificity, was age related, with the highest rate of incorrect negative findings occurring in children under the age of five years [38]. When family history is unavailable or unknown, the distinction of ADPKD from autosomal recessive polycystic kidney disease (ARPKD) may be difficult in children. The presence of renal enlargement is universal in ADPKD, and a positive finding in a renal ultrasound of the parents (when possible) helps the pediatrician make the diagnosis.

With the practice of routine prenatal screening by ultrasonography, some children have been diagnosed with ADPKD in utero. In that setting the most common abnormalities are enlarged hyperechogenic kidneys with increased corticomedullary differentiation [39]. Similar findings have been described in ARPKD, Bardet–Biedl syndrome, Meckel–Gruber syndrome and Ivemark II syndrome. Unlike ADPKD and ARPKD, the latter syndromes are usually accompanied by characteristic extra-renal malformations, which facilitates their diagnosis [40]. The differentiation between the dominant and recessive forms of PKD prenatally is more challenging; however, in utero, ARPKD kidneys are hyperechogenic but tend to be larger than ADPKD kidneys and display decreased corticomedullary differentiation [41]. Beyond 1–2 years of age renal size decreases in ARPKD patients, and nephromegaly becomes a more specific feature of ADPKD. The presence of hepatic cysts in young adults is pathognomonic for ADPKD, while the characteristic sonographic features of Caroli's disease or hepatic fibrosis are virtually diagnostic of ARPKD [42]. In utero the presence of cysts and very early onset disease in ADPKD was thought to be related to maternal inheritance of the mutation and to carry a poor prognosis. However, a recent large study has refuted both notions [41]. The most reliable prognostic factor for infant survival is the level of amniotic fluid, with normal amniotic fluid levels portending a good prognosis [43]. More recently, elevated concentrations of fetal serum β2-microglobulin and cystatin C were found to be associated with poor post-natal renal function in patients with hyperechoic kidneys and could be used as prognostic markers [44].

Since the sequencing of both genes responsible for PKD, genetic screening of at-risk individuals has become possible and could be considered when the radiologic findings are controversial or when the diagnosis is crucial, as in the case of organ donation. Mutations in *PKD1* and *PKD2* genes have been detected by direct sequencing as well as gene linkage analysis. The detection of *PKD1* mutations is particularly challenging, because of the presence of PKD1 pseudogenes (HG) upstream of the actual gene [19]. Mutations are usually unique within a family, and most are nonsense or frameshift mutations leading to the production of a truncated protein. Denaturing high-performance liquid chromatography (DHPLC) screening for *PKD1* and *PKD2* mutations demonstrates a detection rate of approximately 70% [45]. Within families with the *PKD1* gene, a genotype/phenotype correlation has been established with mutations at the 5' end of the gene imparting a worse prognosis with earlier onset of ESRD and a higher risk of cerebral

aneurysms [19]. No such genotype/phenotype correlation has been found for *PKD2* mutations. PKD2, however, imparts a milder disease than PKD1.

Progression of ADPKD

Despite the major anatomical changes that take place in the kidneys as a result of cyst growth and expansion, patients and, in particular, children maintain normal renal function for years. Therefore, surrogate markers of disease progression more sensitive than creatinine clearance or serum creatinine have been sought. In a longitudinal ultrasound study of children <18 years old, Fick-Brosnahan et al. noted that age-matched children with ADPKD have bigger kidneys than unaffected siblings. Over time, the number of cysts in affected children increases significantly and leads to increased renal volume. The rate of renal growth is faster in those with ADPKD than in healthy controls [11].

In recent years magnetic resonance imaging (MRI) was used in the Consortium for Radiologic Studies of Polycystic Kidney Disease (CRISP) in 241 patients ages 15–46 years with normal glomerular filtration rates (GFRs), with yearly imaging studies and clinical evaluations for 3 years. Average baseline renal volume was four-times the normal size, and, during a 3-year follow-up period, renal and cystic volumes increased, on average, by 204±246 ml and 218± 263 ml, respectively. Baseline renal volume correlated negatively with renal function and age. The greatest GFR loss (5 ml/min per year) was detected in patients older than 30 years who had a baseline renal volume of >1,500 ml [46]. A sub-analysis of the CRISP data looked at the significance of *PKD1* vs *PKD2* mutations on the rate of renal growth. There was no difference in percent change in total and cystic renal volume between patients with the *PKD1* gene and those with the *PKD2* gene; however, cyst number was greater in PKD1 kidneys than in PKD2 kidneys. Genotype therefore likely determines cyst initiation, while other factors influence cyst expansion [47].

Longitudinal studies in children revealed information similar to the CRISP data: children with severe renal disease at baseline (defined as a renal volume > 25% above the mean volume for age) had a more profound age-adjusted renal enlargement per year, 26±3 ml vs 11±2 ml [11]. Enlarged kidneys at baseline also correlated with severe disease, with early onset of hypertension and deterioration in renal function on follow-up [48].

Therapeutic approaches to ADPKD

Traditionally, the treatment of ADPKD has focused on complications: hypertension, pain, hematuria, infections of the urinary tract and nephrolithiasis to name a few. The etiology of hypertension remains controversial; however, some research suggests it is driven by activation of the renin–angiotensin–aldosterone system (RAAS), due to the ischemic injury of renal parenchyma by expanding cysts [49]. Clinical studies of the RAAS in hypertensive ADPKD patients have yielded conflicting results [50, 51]. There are ongoing studies to determine whether angiotensin-converting enzyme (ACE) inhibitors will affect cyst growth in children. Researchers at the Children's Hospital in Colorado are studying children and young adults 4 to 21 years of age with normal renal function who are divided into three groups. Group 1 have hypertension (BP > 95th percentile for age and gender), group 2 have BP higher than the 75th percentile, and group 3 have severe renal disease defined by ≥10 cysts and BP between the 25th and the 75th percentile. Each group will be randomly allocated to receive placebo or lisinopril and followed for 5 years. The primary outcome of this study is the rate of change in renal volume assessed by MRI [52]. A larger National Institutes of Health (NIH) funded randomized control trial (HALT PKD Clinical Trial Network) is underway to explore the role of inhibition of the RAAS utilizing combined therapy with angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) in the treatment of hypertensive individuals with ADPKD.

More recently, a multitude of agents that impact cystogenesis have been studied in animal models of PKD. Often these therapeutics need to be used early in the course of the disease and possibly for life. This raises the issue of safety in humans, with particular concern for use in childhood during a critical period of growth and development, as well as concern for potential side effects from long-term exposure to these agents. One inhibitor of cell growth and proliferation that has potential therapeutic value is sirolimus, an inhibitor of the mammalian target of rapamycin (mTOR) that is widely used in transplant recipients. Shillingford et al. demonstrated that polycystin 1 interacts with tuberin, the protein product of the tuberosclerosis 2 gene (*TSC2*). Tuberin abnormalities lead to the development of tuberous sclerosis, a disease with multiorgan involvement including cystic kidney manifestations [53]. The interaction of polycystin 1 and tuberin leads to the inhibition of mTOR. In the case of ADPKD the functional interaction of polycystin 1 and tuberin is disrupted, leading to activation of mTOR, which, in turn, promotes cell hyperplasia and dedifferentiation [54]. Because of its antiproliferative effect, researchers have looked at the effect of sirolimus (rapamycin), injected intraperitoneally, on cyst formation and disease progression in a rat model of ADPKD. Using heterozygote Han:SPRD rats, Tao et al. demonstrated that sirolimus-treated animals had smaller kidneys, with lower cyst volume density, and a decreased

proliferation index in both cystic and non-cystic tubules. Sirolimus also successfully prevented the rise in blood urea nitrogen in these animals [55]. Another group of researchers from Switzerland came to the same conclusions, treating Han:SPRD rats with rapamycin orally [56]. Rapamycin has been approved by the Food and Drug Administration (FDA) and is currently used as part of the immunosuppressive regimen for kidney transplantation. Despite its hematopoietic toxicity, it is a relatively safe drug and has been used in children as well. Treatment studies are now underway in adults with ADPKD to determine if rapamycin is effective in slowing the progression of disease. If the findings are positive, extending its use to children with PKD at high risk of progression would be the next step.

Vasopressin V2 receptor antagonists are also demonstrating potential therapeutic benefits in ADPKD. The potential role for vasopressin in ADPKD progression has been suggested by observations that plasma levels of vasopressin are elevated more so in hypertensive than in normotensive ADPKD patients. Patients and animal models of polycystic kidney disease have a urine concentrating defect, which, in the face of elevated vasopressin levels and up-regulation of aquaporin 2, implies a defect distal to the production of aquaporin 2 [57]. At the molecular level, vasopressin is known to activate adenylate cyclase, and, hence, it increases cAMP levels. The latter plays a pivotal role in cystogenesis, promoting both epithelial cell proliferation and Cl^- excretion, resulting in cyst expansion. The V2 receptor antagonist (OPC31260) was first studied in animal models of ARPKD and nephronophthisis. In both disease entities OPC31260 was found to inhibit disease progression when given early and when given late in the course of disease in these animal models [58]. Next, an antagonist that is more potent and selective to the human V2 receptor (OPC41061) was studied in a mouse model of polycystic kidney disease and was shown to delay the progression of PKD [59]. The biggest advantage of OPC41061, or tolvaptan, is that it has been used as an aquaretic in the treatment of congestive heart failure in humans and has been found to be safe and well tolerated. In a recent phase IIB pilot study, tolvaptan was tested in volunteers with ADPKD and was found to be tolerated and safe at different doses [60]. Studies investigating the effect of tolvaptan on the progression of cystic growth in patients with ADPKD are currently under way. Although the major side effects of tolvaptan (thirst and polyuria) are usually well tolerated by adults, the use of a V2 receptor antagonist in children may be challenging, with access to water being more restricted and enuresis a potential concern.

Other therapies for ADPKD that have been explored include somatostatin, a known inhibitor of Cl^- excretion that could be a promising agent in slowing down cyst expansion in ADPKD. Patients treated with octreotide (a long-acting somatostatin analog) for 6 months had less increase in renal volume as determined by CT [61]. The drug has a good safety profile; however, a few potential side effects are worth mentioning, including an increased risk of gallstones as well as glucose intolerance. As with all other therapies being investigated for the treatment of ADPKD, the earlier they are started the bigger their potential impact on disease progression. In the case of octreotide, its use in childhood would likely be prohibited, given its known inhibitory effect on the release of growth hormone.

Because of the role of EGF in epithelial hyperplasia, leading to cyst formation, an inhibitor of EGFR tyrosine kinase activity was studied in a mouse model of ARPKD. Affected animals were treated with intraperitoneal injections of the inhibitor and were found to have reduced growth and expansion of renal cysts. They were able to maintain normal renal function and survived longer than affected but untreated animals [62]. This same tyrosine kinase inhibitor was also studied in the Han:SPRD rats, a well-established rat model of ADPKD. Here again, the blocking of EGFR activity resulted in a marked reduction in cystogenesis. In both studies no obvious toxic effects were observed [63].

More recently, triptolide, a pro-apoptotic natural product used in traditional Chinese medicine, was investigated. In vitro studies suggest that polycystin 2 may be a binding protein for triptolide and that the interaction between the two leads to Ca^{2+} release. This, in turn, prevents cell proliferation and leads to decreased cystic burden in a murine model of ADPKD [64]. Although our knowledge about triptolide is still embryonic, the potential implications for such findings are huge.

Conclusion

Since the discovery of the *PKD1* and *PKD2* genes, significant advances in the understanding of ADPKD have been made. Years of effort and hard work in the scientific community have slowly put together the pieces of the puzzle linking the protein product of the two genes to the molecular pathways leading to disease development and progression. The pathognomonic feature of ADPKD is the innumerable cysts that replace the normal renal parenchyma, leading to an irreversible decline in renal function and ultimately to ESRD. Cyst development starts very early in life and even perhaps in utero. Advances in imaging techniques and their sensitivities have confirmed that fact. Being able to identify individuals with severe disease and poor prognosis makes the need for effective therapy even more pertinent. Now that we can diagnose the disease with better accuracy, can we offer patients any therapy that would change their course? Affected children remain at the core of this controversy, as early disease detection has,

traditionally, led to problems with insurability and later employment but has offered these individuals little, if any, consolation in terms of treatment options.

In the past 10 years new potential targets for therapies, stemming from animal and bench research, have surfaced, giving hope to millions of disease sufferers. Although the translation of these discoveries into meaningful safe remedies in humans will take time and scrutiny, it is likely that children with ADPKD will benefit from those outstanding scientific contributions in the near future.

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