LEADING ARTICLE

Drugs 2004; 64 (12): 1285-1294
0012-6667/04/0012-1285/$34.00/0

Recent Advances in Understanding the Pathogenesis of Polycystic Kidney Disease

Therapeutic Implications

Benjamin D. Cowley Jr

University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma, USA

Abstract

Hereditary polycystic kidney disease (PKD) is a common cause of renal failure. Increasing knowledge is available regarding mechanisms of cyst development and progression, and renal functional deterioration in PKD. On the basis of this information and theories regarding the pathophysiology of these processes, studies to alter progression and potentially treat PKD have been reported. Cyst development and progression requires epithelial cell proliferation, transepithelial fluid secretion and extracellular matrix remodelling. Several interventions designed to inhibit cell proliferation or alter fluid secretion modify the progression of PKD in selected animal models. Renal functional deterioration appears to involve interstitial inflammation and fibrosis, and tubular apoptosis. Glucocorticoids with anti-inflammatory and antifibrotic properties slow the progression of cystic disease and renal functional deterioration in animal models of PKD. Other interventions, such as dietary modification and angiotensin antagonism, shown to be of benefit in non-PKD models of slowly progressive renal disease, are also of benefit in animal models of PKD. Caution should be used in extrapolating interventional studies in one animal model to another model and certainly to human disease, since examples exist in which treatments in one model of PKD have different effects in another model. Nonetheless, early attempts to determine whether potential treatments are tolerated and of potential benefit in patients with PKD are beginning to appear. Ultimately, treatment of PKD may involve efforts to identify patients at greatest risk for disease progression, thus allowing targeted therapy, use of surrogate markers for disease progression to assist assessment of therapeutic efficacy, and combination therapy to retard disease progression and renal functional deterioration in this common hereditary cause of chronic renal failure.

Autosomal dominant (AD) polycystic kidney disease (PKD) is the most common potentially fatal monogenetic hereditary disease in humans,[1] estimated to affect more than 10 million people worldwide. Although the most striking and consistent pathology occurs in the kidneys, ADPKD is also associated with abnormalities in the liver, heart valves, vascular system, gastrointestinal tract and other organs.[1] Autosomal recessive (AR) PKD is rare, but is also a multiorgan disease with significant pathology seen in the lungs and liver. In both ADPKD and ARPKD, kidneys become grossly distorted by epithelial-lined, fluid-filled cysts which originate as dilations of renal tubules. Significant

progress has been made in identifying the genes responsible for ADPKD[2-5] and ARPKD,[5-7] and understanding the pathophysiological mechanisms of renal cyst formation.[8,9] Studies focusing on mechanisms of progressive renal dysfunction in ADPKD are beginning to appear.[10] Using this pathophysiological information, reports of potential treatments to retard cyst formation and growth, and to delay renal dysfunction in ADPKD have appeared. This article focuses on hereditary PKD and reviews mechanisms of cyst progression and renal dysfunction in ADPKD, identifies potential targets for treatment strategies to retard these processes, discusses selected animal and human studies, considers reasonable current treatment and anticipates future avenues for research. For recommendations regarding treatment of other medical complications of hereditary PKD, as well as acquired renal cystic disease and other forms of renal cystic disease, the reader should consult relevant monographs and book chapters.[11-13]

Human ADPKD is associated with renal cyst development in essentially all cases; however, it should be emphasised that severe renal dysfunction occurs in only approximately 50% of affected individuals. Thus, factors other than the primary genetic defect are important in causing progressive renal dysfunction in ADPKD. Furthermore, glomerular filtration may be remarkably well preserved in patients with ADPKD, despite significant anatomic distortion of kidneys. Therefore, we make a distinction between cyst progression and functional deterioration in ADPKD. Of note, since ADPKD is so common, medical costs are estimated to be billions of dollars worldwide.[1] Thus, interventions that alter disease progression, even incrementally, have the potential to result in considerable savings.

1. Mechanisms of Polycystic Kidney Disease (PKD)

1.1 Cyst Initiation and Progression

In hereditary PKD, the initiating event is genetic mutation. In humans, ADPKD can be caused by mutation in at least two genes, *PKD1*, accounting for approximately 85% of cases, and *PKD2*, accounting for approximately 10% of cases.[2-5] Evidence suggests that mutations in *PKD2* cause a milder form of ADPKD than that caused by mutations in *PKD1*.[10] Limited reports have documented families with ADPKD not linked to *PKD1* or *PKD2*, leading to speculation that mutations in one or more other loci can cause ADPKD.[14-17] Polycystin-1, the novel protein encoded by *PKD1*, has as yet undefined functions. Polycystin-1 is large (~400 kDa), appears to be an integral membrane protein and contains extracellular regions suggesting a role in cell-cell or cell-matrix interactions.[5] Polycystin-1 is thought to contain 11 transmembrane-spanning domains, contains intracellular regions that could function in several different types of signal transduction pathways and a putative coiled-coil region through which it is thought to interact with polycystin-2, the protein encoded by *PKD2*.[5] Polycystin-2 is smaller (~140 kDa) than polycystin-1, but is also an integral membrane protein with undefined functions, though it can serve as a cation channel with some selectivity for calcium.[5] Recent studies suggest that both polycystin-1 and -2 localise to cilia in normal kidney, though their role in ciliary structure or function is unclear.[18] More recently, the gene responsible for ARPKD has been cloned. The encoded protein,[6,7,19] termed fibrocystin or polyductin, is of unknown function but, interestingly, also localises to cilia in normal kidney.

Regardless of the type of PKD, studies using human kidneys, animal models of PKD and cell culture have defined three fundamental pathophysiological mechanisms requisite for the development and progression of PKD: cell proliferation, fluid secretion and extracellular matrix remodelling. It has been shown that cell size does not change appreciably in PKD,[20] thus, cell proliferation is required for progressive cyst growth. Although cyst growth may progress slowly and require only modest increases in cell proliferation, several lines of evidence have supported the presence of increased cell proliferation in animal and human PKD.[21] As long as cysts remain in continuity with tubules, intracystic fluid can originate by glomerular filtration. Since some cysts (the majority in human ADPKD[20]) lose their connections to tubules, as these cysts expand, transepithelial fluid secretion is required to fill the cyst lumens. Although tubular epithelium typically absorbs fluid, numerous studies

have supported the presence of fluid secretion in PKD[21] and have suggesting a role for 3′,5′ cyclic adenosine monophosphate (cAMP) in this process.[21] Furthermore, studies have demonstrated, in fluid from human ADPKD cysts, the presence of an unidentified lipid factor that promotes transepithelial fluid secretion.[22] Finally, cyst expansion requires remodelling of the extracellular matrix. In this regard, studies have shown abnormal expression of matrix metalloproteinases and tissue inhibitors of metalloproteinases in human and animal PKD.[23-28]

In addition to the above fundamental mechanisms, other processes have been implicated in cyst progression in PKD. Histological, ultrastructural and molecular evidence has been consistent with developmental dedifferentiation or misdifferentiation in cystic kidneys. In this regard, some studies have suggested mislocalisation, or at least loss of polarised expression, of proteins typically segregated in tubular epithelial cells,[29,30] although this is not uniformly seen in all models,[31-34] suggesting that loss of polarity may reflect cellular dedifferentiation and is not requisite for cyst formation. Although all cells in patients with ADPKD contain one mutated PKD allele (homozygous human ADPKD has never been reported), only a small percentage of nephrons become cystic. Several mechanisms have been suggested to explain this phenomenon, most prominently the proposal that initiation of cystic transformation requires mutation in the second, normal PKD allele.[35] Factors that predispose to DNA mutations could potentially accelerate the occurrence of this 'second hit'. Although only a small percentage of tubules become cystic, tubular loss appears to be out of proportion to this small percentage of cystic tubules. Efforts to explain this phenomenon resulted in the description of increased apoptosis in cystic kidneys.[36] While some tubules show evidence of obstruction from hyperproliferative tubular epithelium, there does not appear to be abnormal compliance of tubular basement membranes leading to tubular dilatation;[37] furthermore, cysts develop in unobstructed tubules, a finding that is of particular relevance in animal models of PKD in which only a minority of tubules show evidence of obstruction.

1.2 Progression of Renal Dysfunction

As mentioned in the introduction, although cystic renal distortion is seen in all patients with ADPKD, severe renal dysfunction is seen in only 50% of affected individuals. Thus, factors other than the primary genetic defect may affect the development of renal dysfunction in ADPKD. In an effort to understand these additional factors, selected studies have focused on the mechanisms of progressive renal dysfunction, as opposed to progressive cyst growth, in PKD. As seen in other diseases, progressive renal dysfunction in PKD is associated with the development of interstitial abnormalities, particularly inflammation and fibrosis. In this regard, the same lipid factor from human ADPKD cysts that promotes fluid secretion is also a macrophage chemoattractant.[22] In addition, renal expression of the macrophage chemoattractant osteopontin is increased in PKD in rats,[38] and the chemoattractant monocyte chemoattractant protein-1 (MCP-1) is present in increased amounts in kidneys of rats with PKD[38] and in urine of both rats[39] and humans with PKD.[39,40] Whether chemoattractants, such as MCP-1 or osteopontin, can served as surrogate markers which identify individuals at risk for future functional deterioration will require longitudinal studies. It should be noted that osteopontin is expressed at high levels in normal renal medulla. In many diseases, both renal and non-renal, chronic inflammation is ultimately associated with fibrosis. Fibrotic changes are seen in rodent and human PKD. Furthermore, α-smooth muscle actin, a marker of myofibroblast transformation (a hallmark of fibrosis), is increased in kidneys from rats with PKD.[41]

Vascular abnormalities have also been noted in PKD. Studies of human ADPKD kidneys revealed evidence for angiogenesis and expression of angiogenic factors by cyst cells *in vivo* and *in vitro*.[42] The rich capillary network surrounding cysts may be necessary for cyst growth, similar to more traditional neoplastic diseases, and may play a role in fluid secretion into cysts. The anatomical distortion seen in polycystic kidneys has led to the suggestion that associated vascular distortion results in regional ischaemia. Consistent with this idea, increased activity of the renin-angiotensin system is seen in PKD.[43-47] If ischaemia does exist, it does

not seem to be severe enough to cause necrosis; however, chronic ischaemia may lead to apoptosis (which is increased in PKD, as noted in section 1.1). Tubular apoptosis could explain tubular loss that may have a role in progressive renal dysfunction.

2. Potential Targets for Treatment in PKD

2.1 Retarding Progression of Cystic Disease

The ultimate goal of PKD treatment is restoration of normal protein function. Progress towards this goal is currently hampered by the lack of understanding of polycystins and related proteins. However, knowledge is increasing rapidly on this front. In the meantime, efforts to retard cyst progression will logically focus on the fundamental pathophysiological mechanisms responsible for cyst development and growth. Antiproliferative agents, antisecretory measures, inhibition of metalloproteinases and anti-apoptotic measures could all be proposed as potential interventions for retarding cyst progression. In addition, avoidance of agents, such as mutagens, carcinogens (e.g. cigarette smoke) and oxidants that might promote 'second hits' in ADPKD would seem reasonable. In this regard, oxidant stress has been proposed to have a role in PKD.[48-53]

2.2 Retarding Progression of Renal Dysfunction

Depending upon the nature of the intervention and how it interacts with the PKD phenotype, retardation of cyst progression may not necessarily prevent progressive renal dysfunction. Thus, additional therapy to retard renal functional deterioration may be advantageous and even necessary. Furthermore, since cysts develop and progress over decades, therapy that simply retards renal functional deterioration may have significant merit even in the absence of effective treatments to retard cyst progression. Although the mechanisms responsible for renal functional deterioration in PKD are not yet well understood, based on currently available information one could envision that anti-inflammatory agents (either broadly or narrowly targeted), antifibrotic agents or combinations of these types of agents might be of benefit.

3. Studies in Animal Models of PKD

Numerous studies using animals models have presented evidence that disease progression in hereditary PKD can be altered by dietary and pharmacological interventions (table I). Some studies intentionally worsened disease progression in attempts to understand pathophysiological mechanisms. A greater number have attempted to ameliorate disease progression, in efforts both to understand pathophysiological mechanisms and to explore potential treatments. All of these studies support the idea that factors other than the primary genetic defect are important in determining the rate of cystic disease progression and the rate of renal functional deterioration. In many cases, because of the broad effects of the interventions studied, multiple potential pathophysiological targets may have been affected. In other cases, more narrowly targeted interventions were studied. In general, interventions have been chosen based on studies in other renal diseases, based on theories regarding general pathophysiological mechanisms, or in efforts to target specific mechanisms of potential importance for disease progression. Studies are too numerous to review each in detail; therefore, selected studies are reviewed in this section.

Although increased epithelial cell proliferation has been documented in PKD, the mechanism(s) responsible are not well understood. Several studies have documented abnormalities of epidermal growth factor (EGF) receptor expression in animal and human PKD,[73-75] with loss of normal polarised expression in basolateral membranes. EGF receptors can be activated by circulating EGF or soluble transforming growth factor (TGF)-α, which is produced by cleavage of membrane-bound TGFα. In response to these findings, studies have shown that interference with EGF receptor activation, using an EGF receptor-specific tyrosine kinase inhibitor,[67] ameliorates renal cystic disease in the bpk murine model of autosomal recessive, slowly progressive PKD. More recent studies have confirmed a benefit of EGF receptor blockade in the Han:SPRD rat model of autosomal dominant, slowly progressive PKD.[68]

Early studies to support the concept of increased cellular proliferation in PKD demonstrated increased renal c-myc proto-oncogene expression in

Table I. Selected studies of manipulation of disease progression of polycystic kidney disease (PKD) in animals

Treatment	Model (reference)	Severity of cystic disease	Severity of renal failure
Paclitaxel	cpk mouse[54]	Decreased	Decreased
	pcy mouse[55]	Unchanged	Unchanged
	Han:SPRD rat[55]	Unchanged	Unchanged
	orpk mouse[56]	Unchanged	Unchanged
Methylprednisolone	Han:SPRD rat[57]	Decreased	Decreased
	pcy mouse[57]	Decreased	Decreased
Ammonium chloride loading	Han:SPRD rat[58,59]	Markedly increased	Markedly increased
	pcy mouse[59]	Markedly increased	Markedly increased
Potassium deficient diet	Han:SPRD rat[58]	Markedly increased	Markedly increased
Alkali (sodium or potassium bicarbonate, or potassium citrate)	Han:SPRD rat[59-62] pcy mouse[59,63]	Decreased Increased	Decreased Increased
ACE inhibition	Han:SPRD rat[64,65]	Decreased	Decreased
Angiotensin receptor blockade	Han:SPRD rat[64]	Decreased	Decreased
Lovastatin	Han:SPRD rat[66]	Decreased	Decreased
Probucol	pcy mouse[52]	Decreased	Decreased
Tyrosine kinase inhibition	bpk mouse[67]	Decreased	Decreased
	Han:SPRD rat[68]	Decreased	Decreased
	pck rat[69]	Increased	Increased
c-myc antisense	cpk mouse[70]	Decreased	Decreased
Vasopressin V_2 receptor antagonist	pcy mouse[71]	Decreased	Decreased
	Han:SPRD rat[71]	Decreased	Decreased
Pioglitazone	*PKD1*-KO[72]	Decreased	Not determined

murine and rat PKD.[76,77] In addition, transgenic mice overexpressing c-myc develop renal cystic disease.[78] In response to these findings, treatment with specially derivatized c-myc antisense oligonucleotides has been used to attempt to decrease renal c-myc expression and alter disease progression in murine PKD. Treatment with c-myc antisense oligonucleotide in DBA-cpk/cpk mice with ARPKD resulted in decreased renal c-myc mRNA and protein expression, and ameliorated renal cystic disease as assessed by kidney weight as a proportion of bodyweight and blood urea nitrogen (BUN) concentrations.[70]

Increased expression of RAS proteins, important mediators of cell proliferation, has also been shown in murine PKD.[76] Activation of RAS proteins involves covalent attachment of farnesyl residues, with subsequent migration to the cell membrane. HMG-CoA reductase inhibitors can inhibit production of farnesyl residues and impair RAS activation. HMG-CoA reductase inhibition in Han:SPRD rats, which manifest slowly progressive PKD, ameliorates renal cystic disease as assessed by kidney weight as a proportion of bodyweight and BUN concentrations.[66] HMG-CoA reductase inhibitors have many effects and, thus, the exact mechanism(s) whereby they ameliorate PKD is unclear.

Urinary concentrating defects have been documented in human and animal PKD, and can be an early finding, suggesting that this may not simply be related to anatomical distortion and disruption of medullary osmolality gradients necessary for maximal urinary concentration. In support of this concept, studies in two different murine models of PKD have documented abnormal expression of proteins important in urinary concentration. Both the DBA-cpk/cpk model of rapidly progressive ARPKD and the DBA-pcy/pcy model of slowly progressive ARPKD have increased renal abundance of vasopressin V_2 receptor, aquaporin-2 and aquaporin-3.[79] Increased activity of the V_2 receptor can result in increased cAMP production, which can result in increased fluid secretion and increased cell proliferation.[21] Subsequent studies showed that in the pcy mouse and the Han:SPRD rat, treatment with a V_2 receptor antagonist ameliorated renal cystic disease as assessed by kidney weight as a proportion of bodyweight and cyst volume density.[71]

These interventions were finely targeted, based on proposed pathophysiological mechanisms and specific findings in animal and human studies. Other studies have used more broadly targeted treatments in efforts to alter disease progression. In various models of progressive renal disease, dietary modifications alter disease progression. In Han:SPRD rats, dietary protein restriction ameliorates and dietary protein loading exacerbates cystic disease and renal dysfunction.[58] In addition, replacement of casein-based protein with soy-based protein in Han:SPRD rats ameliorates cystic disease, renal dysfunction and tubulointerstitial inflammation.[80] Furthermore, in Han:SPRD rats, dietary supplementation with flaxseed, which has anti-inflammatory properties of undefined mechanism, ameliorates cystic disease, renal dysfunction and tubulointerstitial inflammation.[81]

In numerous studies using models of non-PKD chronic progressive renal diseases, ACE inhibition ameliorates renal pathology and functional deterioration. It has been proposed that this occurs by decreasing intraglomerular pressure and hyperfiltration; however, it should be noted that angiotensin II is a growth factor for selected cell types found in the kidney. ACE inhibition has been shown to ameliorate disease progression in Han:SPRD rats.[64,65] Whether this occurs by decreasing intraglomerular pressure and hyperfiltration in remaining functioning nephrons, by decreasing growth promoting effects of angiotensin II or by some other undefined mechanism is unclear.

As mentioned in section 1.2, interstitial inflammation is thought to have a role in disease progression in many types of chronic progressive renal disease. Evidence suggests that this may also be true for PKD. Interstitial inflammation has been described in human[82] and rodent ADPKD,[38] inflammatory cell chemoattractants can be isolated from human[40] and rodent polycystic kidneys,[38] and urinary abundance of inflammatory cell chemoattractants is increased in human ADPKD[22,39,40] and rodent ADPKD.[39] Interstitial inflammation and fibrosis correlate with the development of renal dysfunction in both the Han:SPRD rat and DBA-pcy/pcy mouse. Treatment with glucocorticoids markedly ameliorates interstitial inflammation and fibrosis, renal cystic change and renal dysfunction in both of these models of slowly progressive PKD.[57] Glucocorticoids have a multitude of effects and, therefore, conclusions as to the mechanism whereby they ameliorate PKD can not be made. In addition, oxidant stress has been proposed to have a role in the progression of chronic renal diseases, including PKD,[48-53] and antioxidants have been shown to retard PKD in mice.[52]

In models of non-PKD chronic progressive renal disease in which individual pharmacological agents have been shown to alter disease progression, recent studies have shown that combinations of agents are more effective than either alone in ameliorating disease. Use of ACE inhibitors or angiotensin receptor blockers in combination with the immunosuppressant mycophenolate mofetil in remnant kidney disease[83-85] is more effective that the individual agents. Use of an ACE inhibitor plus an HMG-CoA reductase inhibitor in advanced renal disease caused by passive Heymann nephritis and uninephrectomy[86] is more effective than either agent alone. Whether this type of combination therapy will be of benefit in PKD remains to be seen.

Caution should be used in extrapolating interventional studies in one animal model to another untested model and certainly to human disease. Several examples exist in which treatments in one model of PKD had different effects in another. In one of the first studies to demonstrate the ability to alter PKD progression, paclitaxel ameliorated PKD in the C57BL6J-cpk/cpk mouse model of rapidly progressive PKD.[54] Although subsequent studies confirmed this beneficial effect in cpk mice, in Han:SPRD rats there was no beneficial effect and significant toxicity of paclitaxel.[55] Furthermore, paclitaxel was ineffective in altering the progression of PKD in the orpk mouse model of PKD.[56] Initial studies showed a beneficial effect of alkali administration on PKD progression in Han:SPRD rats;[59-62] however, subsequent studies showed a mild detrimental effect in pcy mice.[59,63] As mentioned earlier in this section, EGF receptor-specific tyrosine kinase inhibition is of benefit in bpk mice[67] and Han:SPRD rats;[68] however, the same treatment worsens disease in the pck rat.[69] Finally, although interference with EGF receptor tyrosine kinase function ameliorates disease in bpk mice, exogenous

EGF administration in cpk mice actually ameliorates disease.[87]

4. Clinical Studies in PKD

Several studies have sought to identify risk factors for progression of renal dysfunction in human ADPKD.[88,89] On the basis of these studies, the following characteristics appear to be associated with a greater risk of renal functional deterioration in PKD: early age at diagnosis, hypertension, proteinuria, haematuria, male gender and smoking. These factors are helpful in identifying individuals who are at increased risk for renal dysfunction; however, this information does not help define therapy or advance our understanding of the mechanisms of disease progression. Although kidneys in PKD can develop dramatic anatomical distortion, it is still unclear whether renal size and changes in renal size over time are predictive of future changes in renal function. A National Institutes of Health (NIH)-sponsored trial, the Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease (CRISP), is underway and seeks to answer this question.

Some initial attempts to alter disease progression in human ADPKD have been made or are soon to begin. The Modification of Diet in Renal Disease (MDRD) study enrolled a disproportionate number of patients with PKD.[90] In a subanalysis of these patients it was concluded that, in patients with only marginal renal impairment, neither dietary protein restriction nor a lower blood pressure altered renal functional deterioration.[91] In this same subanalysis, in patients with more severe renal impairment, dietary protein restriction resulted in slightly slower deterioration of renal function.

More recently, a NIH-sponsored trial to evaluate selected therapeutic interventions to retard disease progression, including ACE inhibition, is in the planning stages. This study may produce data that will be helpful in determining more specific therapy to retard cystic disease progression and renal functional deterioration in PKD.

Finally, the initial steps in translating specific targeted therapy from the laboratory to the bedside have begun. Preliminary trials to evaluate the safety of c-myc antisense treatment in patients with ADPKD have been completed and have revealed no serious adverse side effects of this therapy targeted to specific pathophysiological abnormalities demonstrated in animal models of PKD.[92]

If precedents from other diseases translate to PKD, then there is some hope that effective therapies may be developed to at least slow progression of renal dysfunction in human PKD. Recently, investigators reported retardation of renal functional deterioration and amelioration of proteinuria in human renal disease with use of ACE inhibitors, angiotensin II receptor antagonists and HMG-CoA reductase inhibitors.[93] For reasons stated in section 3, ACE inhibitors and angiotensin II receptor antagonists may have beneficial effects independent of decreasing intraglomerular pressures, and HMG-CoA reductase inhibitors may have beneficial effects beyond lipid lowering. Thus, even though glomerular pathology is not prominent in PKD and severe hyperlipidaemia is not a hallmark of PKD, analogous measures might be of benefit.

5. Reasonable Current Treatment in Attempts to Retard Disease Progression

At present, based on studies in humans and animals, there are several interventions that have theoretical potential to retard disease progression and deterioration of renal function, and have minimal potential adverse consequences in patients with PKD. Smoking avoidance has multiple systemic benefits and may have specific benefits in patients with PKD. Although antioxidants have been shown to be of benefit in mice,[52] their role in humans is yet to be defined. Antihypertensive therapy, preferably with an ACE inhibitor or an angiotensin II receptor antagonist, is considered standard care. In view of recent questions regarding non-ACE production of angiotensin II, combination therapy with both an ACE inhibitor and an angiotensin II receptor antagonist may be of additional benefit; however, studies are needed to confirm this. In this regard, it should be noted that recent studies have shown increased chymase, an enzyme capable of catalysing the conversion of angiotensin I to angiotensin II, in human ADPKD kidneys.[94] Even though there was no clear benefit to dietary protein restriction in PKD patients in the MDRD study, many clinicians still recommend modest dietary protein restriction,

citing the relatively short duration of follow up in the MDRD study. Studies have repeatedly shown that cAMP agonists promote fluid secretion across renal epithelial monolayers and, therefore, avoidance of cAMP agonists, such as caffeine, theophylline and related compounds, seems prudent. More speculative is any role for HMG-CoA reductase inhibitors in PKD. Given the well documented beneficial effects of these drugs on cardiovascular disease, routine lipid screening in patients with PKD and use of these drugs in appropriate circumstances may have additional beneficial effects beyond lipid lowering but, once again, studies are needed to confirm this. Finally, in view of the disparate results in different species, treatment with supplemental bicarbonate or bicarbonate precursors should probably be reserved for patients with systemic acidosis.

6. Anticipated Future Avenues

Several areas present clear opportunities to improve specific therapy of patients with PKD. Since PKD progresses over a number of decades, identification of valid surrogate markers for disease progression and future renal functional deterioration will improve the ability to determine whether potential therapies are truly effective and allow targeting of therapies to those at greatest risk. Using advanced, high throughput techniques, pharmaceutical researchers are now able screen large numbers of compounds for efficacy in retarding cyst development and progression *in vitro*, and this approach may increase the number of potential therapies to be tested *in vivo*. As more is learned regarding the functions of polycystins, and how mutations in them disrupt normal cell biology and cellular physiology, this may improve the ability to design therapies based on gene function and specific pathophysiological mechanisms. In the near future, a more definitive determination regarding whether ACE inhibition is of genuine benefit in PKD may be available, since the NIH-sponsored trial of this therapy (see section 4; other potential therapies may be included as subprojects) is anticipated to begin enrolling patients soon. Finally, if studies in animals translate into effective therapies in humans, physicians caring for patients with PKD may borrow a page from the oncologists' handbook and begin speaking of 'combination chemotherapy' in efforts to retard disease progression and renal functional deterioration in this common hereditary cause of chronic renal failure.

Acknowledgements

The author receives support from the University of Oklahoma Foundation as The John Gammill Chair in Polycystic Kidney Disease. Various studies discussed were supported by Baxter Healthcare, The Polycystic Kidney Foundation, The University of Kansas Medical Center Research Institute and The Presbyterian Health Foundation of Oklahoma.

References

1. Martinez JR, Grantham JJ. Polycystic kidney disease: etiology, pathogenesis, and treatment. Dis Mon 1995; 41: 693-765
2. International Polycystic Kidney Disease Consortium. Polycystic kidney disease: the complete structure of the PKD1 gene and its protein. Cell 1995; 81: 289-98
3. American PKD1 Consortium. Analysis of the genomic sequence for the autosomal dominant polycystic kidney disease (PKD1) gene predicts the presence of a leucine-rich repeat. Hum Mol Genet 1995; 4: 575-82
4. Mochizuki T, Wu G, Tomohito H, et al. PKD2, a gene for polycystic kidney disease that encodes an integral membrane protein. Science 1996; 272: 1339-42
5. Harris PC. Molecular basis of polycystic kidney disease: PKD1, PKD2 and PKHD1. Curr Opin Nephrol Hypertens 2002; 11: 309-14
6. Ward CJ, Hogan MC, Rossetti S, et al. The gene mutated in autosomal recessive polycystic kidney disease encodes a large, receptor-like protein. Nat Genet 2002; 30: 259-69
7. Onuchic LF, Furu L, Nagasawa Y, et al. PKHD1, the polycystic kidney and hepatic disease 1 gene, encodes a novel large protein containing multiple immunoglobulin-like plexin-transcription-factor domains and parallel beta-helix 1 repeats. Am J Hum Genet 2002; 70: 1305-17
8. Grantham JJ. The etiology, pathogenesis, and treatment of autosomal dominant polycystic kidney disease: recent advances. Am J Kidney Dis 1996; 28: 788-803
9. Bacallao RL, Carone FA. Recent advances in the understanding of polycystic kidney disease. Curr Opin Nephrol Hypertens 1997; 6: 377-83
10. Grantham JJ, Cowley Jr BD, Torres VE. Progression of autosomal dominant polycystic kidney disease to renal failure. In: Seldin DW, Giebisch G, editors. The kidney: physiology and pathophysiology. Philadelphia (PA): Lippincott, Williams and Wilkins, 2000: 2513-36
11. Gabow PA, Grantham JJ. Polycystic kidney disease. In: Schrier RW, Gottschalk CW, editors. Diseases of the kidney. 6th ed. Boston (MA): Little, Brown, and Co., 1997: 521-60
12. Gile RD, Cowley Jr BD, Grantham JJ. Renal cystic disease. In: Suki WN, Massry SG, editors. Therapy of renal diseases and related disorders. Boston (MA): Kluwer Academic Publishers, 1998: 639-62
13. Cowley Jr BD, Grantham JJ. Renal cystic diseases. In: Brady HR, Wilcox CS, Brenner BM, editors. Therapy in nephrology and hypertension. Philadelphia (PA): WB Saunders Company, 1999: 367-74
14. de Almeida S, de Almeida E, Peters D, et al. Autosomal dominant polycystic kidney disease: evidence for the existence of a third locus in a Portuguese family. Hum Genet 1995; 96: 83-8

15. Daoust MC, Reynolds DM, Bichet DG, et al. Evidence for a third genetic locus for autosomal dominant polycystic kidney disease. Genomics 1995; 25: 733-6
16. Ariza M, Alvarez V, Marin R, et al. A family with a milder form of adult dominant polycystic kidney disease not linked to the PKD1 (16p) or PKD2 (4q) genes. J Med Genet 1997; 34: 587-9
17. Turco AE, Clementi M, Rossetti S, et al. An Italian family with autosomal dominant polycystic kidney disease unlinked to either the PKD1 or PKD2 gene. Am J Kidney Dis 1996; 28: 759-61
18. Ong AC, Wheatley DN. Polycystic kidney disease: the ciliary connection. Lancet 2003; 361: 774-6
19. Nagasawa Y, Matthiesen S, Onuchic LF, et al. Identification and characterization of Pkhd1, the mouse orthologue of the human ARPKD gene. J Am Soc Nephrol 2002; 13: 2246-58
20. Grantham JJ, Geiser JL, Evan AP. Cyst formation and growth in autosomal dominant polycystic kidney disease. Kidney Int 1987; 31: 1145-52
21. Calvet JP, Grantham JJ. The genetics and physiology of polycystic kidney disease. Semin Nephrol 2001; 21: 107-23
22. Grantham JJ, Schreiner GF, Rome L, et al. Evidence for inflammatory and secretagogue lipids in cyst fluids from patients with autosomal dominant polycystic kidney disease. Proc Assoc Am Physicians 1997; 109: 397-408
23. Obermuller N, Morente N, Kranzlin B, et al. A possible role for metalloproteinases in renal cyst development. Am J Physiol Renal Physiol 2001; 280: F540-50
24. Nakamura T, Ushiyama C, Suzuki S, et al. Elevation of serum levels of metalloproteinase-1, tissue inhibitor of metalloproteinase-1 and type IV collagen, and plasma levels of metalloproteinase-9 in polycystic kidney disease. Am J Nephrol 2000; 20: 32-6
25. Rankin CA, Itoh Y, Tian C, et al. Matrix metalloproteinase-2 in a murine model of infantile-type polycystic kidney disease. J Am Soc Nephrol 1999; 10: 210-7
26. Rankin CA, Suzuki K, Itoh Y, et al. Matrix metalloproteinases and TIMPS in cultured C57BL/6J-cpk kidney tubules. Kidney Int 1996; 50: 835-44
27. Schaefer L, Han X, Gretz N, et al. Tubular gelatinase A (MMP-2) and its tissue inhibitors in polycystic kidney disease in the Han: SPRD rat. Kidney Int 1996; 49: 75-81
28. Schaefer L, Han X, Gretz N, et al. Alterations of cathepsins B, H and L in proximal tubules from polycystic kidneys of the Han: SPRD rat. Kidney Int 1996; 50: 424-31
29. Wagner MC, Molitoris BA. Renal epithelial polarity in health and disease. Pediatr Nephrol 1999; 13: 163-70
30. Wilson PD. Epithelial cell polarity and disease. Am J Physiol 1997; 272: F434-42
31. Obermuller N, Gretz N, Kriz W, et al. Differentiation and cell polarity during renal cyst formation in the Han: SPRD (cy/+) rat, a model for ADPKD. Am J Physiol 1997; 273: F357-71
32. Brill SR, Ross KE, Davidow CJ, et al. Immunolocalization of ion transport proteins in human autosomal dominant polycystic kidney epithelial cells. Proc Natl Acad Sci U S A 1996; 93: 10206-11
33. Barisoni L, Trudel M, Chretien N, et al. Analysis of the role of membrane polarity in polycystic kidney disease of transgenic SBM mice. Am J Pathol 1995; 147: 1728-35
34. Kawa G, Nagao S, Yamamoto A, et al. Sodium pump distribution is not reversed in the DBA/2FG-pcy, polycystic kidney disease model mouse. J Am Soc Nephrol 1994; 4: 2040-9
35. Germino GG. Autosomal dominant polycystic kidney disease: a two-hit model. Hosp Pract (Off Ed) 1997; 32: 81-2, 85
36. Kovacs J, Gomba S. Analysis of the role of apoptosis and cell proliferation in renal cystic disorders. Kidney Blood Press Res 1998; 21: 325-8
37. Grantham JJ, Donoso VS, Evan AP, et al. Viscoelastic properties of tubule basement membranes in experimental renal cystic disease. Kidney Int 1987; 32: 187-97
38. Cowley Jr BD, Ricardo SD, Nagao S, et al. Increased renal expression of monocyte chemoattractant protein-1 and osteopontin in autosomal dominant polycystic kidney disease in rats. Kidney Int 2001; 60: 2087-96
39. Nagao S, Wolfe AM, Sise CL, et al. Elevated urinary monocyte chemoattractant protein-1 in human and rodent autosomal dominant polycystic kidney disease [abstract]. J Am Soc Nephrol 1999; 10: 421A
40. Zheng D, Wolfe M, Cowley Jr BD, et al. Urinary excretion of monocyte chemoattractant protein-1 in autosomal dominant polycystic kidney disease. J Am Soc Nephrol 2003; 14 (10): 2588-95
41. Cowley Jr BD, Ricardo SD, Diamond JR. Elevated proinflammatory chemokines in autosomal dominant polycystic kidney disease (ADPKD) [abstract]. J Am Soc Nephrol 1996; 7: 1595
42. Bello-Reuss E, Holubec K, Rajaraman S. Angiogenesis in autosomal-dominant polycystic kidney disease. Kidney Int 2001; 60: 37-45
43. Braun C, Kleemann T, Hilgenfeldt U, et al. Activity and functional significance of the renal kallikrein-kinin-system in polycystic kidney disease of the rat. Kidney Int 2002; 61: 2149-56
44. Ecder T, Edelstein CL, Chapman AB, et al. Reversal of left ventricular hypertrophy with angiotensin converting enzyme inhibition in hypertensive patients with autosomal dominant polycystic kidney disease. Nephrol Dial Transplant 1999; 14: 1113-6
45. Cerasola G, Li Vecchi M, Mule G, et al. Role of renin-angiotensin-aldosterone system and of sympathetic activity in arterial hypertension associated with autosomal dominant polycystic kidney disease. Contrib Nephrol 1997; 122: 22-7
46. Wang D, Strandgaard S. The pathogenesis of hypertension in autosomal dominant polycystic kidney disease. J Hypertens 1997; 15: 925-33
47. Parfrey PS, Barrett BJ. Hypertension in autosomal dominant polycystic kidney disease. Curr Opin Nephrol Hypertens 1995; 4: 460-4
48. Korsmeyer SJ, Shutter JR, Veis DJ, et al. Bcl-2/Bax: a rheostat that regulates an anti-oxidant pathway and cell death. Semin Cancer Biol 1993; 4: 327-32
49. Zima T, Crkovska J, Merta M, et al. Activity of the antioxidant enzyme, glutathione peroxidase, on autosomal dominant polycystic kidney disease patients. Biochem Mol Biol Int 1995; 35: 699-704
50. Maser RL, Cavlet JP. Reduced expression of antioxidant and detoxicant enzyme genes in polycystic kidney disease (PKD) [abstract]. J Am Soc Nephrol 1996; 7: 1617
51. Iakoubova OA, Pacella LA, Her H, et al. LTW4 protein on mouse chromosome 1 is a member of a family of antioxidant proteins. Genomics 1997; 42: 474-8
52. Nagao S, Yamaguchi T, Kasahara M, et al. Effect of probucol in a murine model of slowly progressive polycystic kidney disease. Am J Kidney Dis 2000; 35: 221-6
53. Maser RL, Vassmer D, Magenheimer BS, et al. Oxidant stress and reduced antioxidant enzyme protection in polycystic kidney disease. J Am Soc Nephrol 2002; 13: 991-9
54. Woo DD, Miao SY, Pelayo JC, et al. Taxol inhibits progression of congenital polycystic kidney disease. Nature 1994; 368: 750-3
55. Martinez JR, Cowley BD, Gattone VH, et al. The effect of paclitaxel on the progression of polycystic kidney disease in rodents. Am J Kidney Dis 1997; 29: 435-44
56. Sommardahl CS, Woychik RP, Sweeney WE, et al. Efficacy of taxol in the orpk mouse model of polycystic kidney disease. Pediatr Nephrol 1997; 11: 728-33

57. Gattone II VH, Cowley Jr BD, Barash BD, et al. Methylprednisolone retards the progression of inherited polycystic kidney disease in rodents. Am J Kidney Dis 1995; 25: 302-13
58. Cowley Jr BD, Grantham JJ, Muessel MJ, et al. Modification of disease progression in rats with inherited polycystic kidney disease. Am J Kidney Dis 1996; 27: 865-79
59. Torres VE, Cowley Jr BD, Branden MG, et al. Long-term ammonium chloride or sodium bicarbonate treatment in two models of polycystic kidney disease. Exp Nephrol 2001; 9: 171-80
60. Torres VE, Mujwid DK, Wilson DM, et al. Renal cystic disease and ammoniagenesis in Han: SPRD rats. J Am Soc Nephrol 1994; 5: 1193-200
61. Tanner GA. Potassium citrate/citric acid intake improves renal function in rats with polycystic kidney disease. J Am Soc Nephrol 1998; 9: 1242-8
62. Tanner GA, Tanner JA. Citrate therapy for polycystic kidney disease in rats. Kidney Int 2000; 58: 1859-69
63. Tanner GA, Vijayalakshmi K, Tanner JA. Effects of potassium citrate/citric acid intake in a mouse model of polycystic kidney disease. Nephron 2001; 84: 270-3
64. Keith DS, Torres VE, Johnson CM, et al. Effect of sodium chloride, enalapril, and losartan on the development of polycystic kidney disease in Han: SPRD rats. Am J Kidney Dis 1994; 24: 491-8
65. Ogborn MR, Sareen S, Pinette G. Cilazapril delays progression of hypertension and uremia in rat polycystic kidney disease. Am J Kidney Dis 1995; 26: 942-6
66. Gile RD, Cowley Jr BD, Gattone II VH, et al. Effect of lovastatin on the development of polycystic kidney disease in the Han: SPRD rat. Am J Kidney Dis 1995; 26: 501-7
67. Sweeney WE, Chen Y, Nakanishi K, et al. Treatment of polycystic kidney disease with a novel tyrosine kinase inhibitor. Kidney Int 2000; 57: 33-40
68. Torres VE, Sweeney Jr WE, Wang X, et al. EGF receptor tyrosine kinase inhibition attenuates the development of PKD in Han: SPRD rats. Kidney Int 2003; 64 (5): 1573-9
69. Torres VE, Sweeney Jr WE, Wang X, et al. Epidermal growth factor receptor tyrosine kinase inhibition is not protective in PCK rats. Kidney Int. In press
70. Ricker JL, Mata JE, Iverson PI, et al. c-myc antisense oligonucleotide treatment ameliorates murine ARPKD. Kidney Int 2002; 61 (1): S125-31
71. Gattone VH, Wang X, Harris PC, et al. Inhibition of renal cystic disease development and progression by a vasopressin V2 receptor antagonist. Nat Med 2003; 10: 1323-6
72. Muto S, Aiba A, Saito Y, et al. Pioglitazone improves the phenotype and molecular defects of a targeted Pkd1 mutant. Hum Mol Genet 2002; 11: 1731-42
73. Du J, Wilson PD. Abnormal polarization of EGF receptors and autocrine stimulation of cyst epithelial growth in human ADPKD. Am J Physiol 1995; 269: C487-95
74. Richards WG, Sweeney WE, Yoder BK, et al. Epidermal growth factor receptor activity mediates renal cyst formation in polycystic kidney disease. J Clin Invest 1998; 101: 935-9
75. Sweeney Jr WE, Avner ED. Functional activity of epidermal growth factor receptors in autosomal recessive polycystic kidney disease. Am J Physiol 1998; 275: F387-94
76. Cowley Jr BD, Chadwick LJ, Grantham JJ, et al. Elevated proto-oncogene expression in polycystic kidneys of the C57BL/6J (cpk) mouse. J Am Soc Nephrol 1991; 1: 1048-53
77. Cowley Jr BD, Gudapaty S, Kraybill AL, et al. Autosomal dominant polycystic kidney disease in the rat. Kidney Int 1993; 43: 522-34
78. Trudel M, D'Agati V, Costantini F. c-myc as an inducer of polycystic kidney disease in transgenic mice. Kidney Int 1991; 39: 665-71
79. Gattone VH, Maser RL, Tian C, et al. Developmental expression of urine concentration-associated genes and their altered expression in murine infantile-type polycystic kidney disease. Dev Genet 1999; 24: 309-18
80. Ogborn MR, Nitschmann E, Weiler HA, et al. Modification of polycystic kidney disease and fatty acid status by soy protein diet. Kidney Int 2000; 57: 159-66
81. Ogborn MR, Nitschmann E, Weiler H, et al. Flaxseed ameliorates interstitial nephritis in rat polycystic kidney disease. Kidney Int 1999; 55: 417-23
82. Zeier M, Fehrenbach P, Geberth S, et al. Renal histology in polycystic kidney disease with incipient and advanced renal failure. Kidney Int 1992; 42: 1259-65
83. Noris M, Azzollini N, Pezzotta A, et al. Combined treatment with mycophenolate mofetil and an angiotensin II receptor antagonist fully protects from chronic rejection in a rat model of renal allograft. J Am Soc Nephrol 2001; 12: 1937-46
84. Fujihara CK, De Lourdes Noronha I, Malheiros DM, et al. Combined mycophenolate mofetil and losartan therapy arrests established injury in the remnant kidney. J Am Soc Nephrol 2000; 11: 283-90
85. Remuzzi G, Zoja C, Gagliardini E, et al. Combining an antiproteinuric approach with mycophenolate mofetil fully suppresses progressive nephropathy of experimental animals. J Am Soc Nephrol 1999; 10: 1542-9
86. Zoja C, Corna D, Rottoli D, et al. Effect of combining ACE inhibitor and statin in severe experimental nephropathy. Kidney Int 2002; 61: 1635-45
87. Gattone II VH, Lowden DA, Cowley Jr BD. Epidermal growth factor ameliorates autosomal recessive polycystic kidney disease in mice. Dev Biol 1995; 169: 504-10
88. Johnson AM, Gabow PA. Identification of patients with autosomal dominant polycystic kidney disease at highest risk for end-stage renal disease. J Am Soc Nephrol 1997; 8: 1560-7
89. Orth SR, Stockmann A, Conradt C, et al. Smoking as a risk factor for end-stage renal failure in men with primary renal disease. Kidney Int 1998; 54: 926-31
90. Klahr S, Levey AS, Beck GJ, et al. The effects of dietary protein restriction and blood-pressure control on the progression of chronic renal disease: Modification of Diet in Renal Disease Study Group. N Engl J Med 1994; 330: 877-84
91. Klahr S, Breyer JA, Beck GJ, et al. Dietary protein restriction, blood pressure control, and the progression of polycystic kidney disease: Modification of Diet in Renal Disease Study Group. J Am Soc Nephrol 1995; 5: 2037-47
92. Clinical trial supports further study of AVI's NEUGENE Antisense in polycystic kidney disease patients [abstract; online]. Available from URL: www avibio.com [Accessed 2004 Apr 25]
93. Bianchi S, Bigazzi R, Caiazza A, et al. A controlled, prospective study of the efects of atorvastatin on proteinuria and progression of kidney disease. Am J Kidney Dis 2003; 41: 565-70
94. McPherson EA, Luo Z, Brown RA, et al. Chymase-like angiotensin II-generating activity in end-stage human autosomal dominant polycystic kidney disease. J Am Soc Nephrol 2004; 15: 493-500

Correspondence and offprints: Prof. *Benjamin D. Cowley*, Jr, Nephrology/WP2250, University of Oklahoma Health Sciences Center, 920 Stanton L. Young Blvd, Oklahoma City, OK 73104, USA.
E-mail: Ben-Cowley@ouhsc.edu