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invited review

Murine models of polycystic kidney disease: molecular and therapeutic insights

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Guay-Woodford, Lisa M. Murine models of polycystic kidney disease: molecular and therapeutic insights. *Am J Physiol Renal Physiol* 285: F1034–F1049, 2003; 10.1152/ajprenal.00195.2003.—Numerous murine (mouse and rat) models of polycystic kidney disease (PKD) have been described in which the mutant phenotype results from a spontaneous mutation or engineering via chemical mutagenesis, transgenic technologies, or gene-specific targeting in mouse orthologs of human PKD genes. These murine phenotypes closely resemble human PKD, with common abnormalities observed in tubular epithelia, the interstitial compartment, and the extracellular matrix of cystic kidneys. In both human and murine PKD, genetic background appears to modulate the renal cystic phenotype. In murine models, these putative modifying effects have been dissected into discrete factors called quantitative trait loci and genetically mapped. Several lines of experimental evidence support the hypothesis that PKD genes and their modifiers may define pathways involved in cystogenesis and PKD progression. Among the various pathway abnormalities described in murine PKD, recent provocative data indicate that structural and/or functional defects in the primary apical cilia of tubular epithelia may play a key role in PKD pathogenesis. This review describes the most widely studied murine models; highlights the data regarding specific gene defects and genetic modifiers; summarizes the data from these models that have advanced our understanding of PKD pathogenesis; and examines the effect of various therapeutic interventions in murine PKD.

autosomal dominant polycystic kidney disease; autosomal recessive polycystic kidney disease; polycystic kidney disease quantitative trait loci; polycystic kidney disease therapeutics

RENAL TUBULAR CYSTS DEVELOP in several inherited human disorders. Among these, the polycystic kidney diseases (PKD) are one of the leading causes of end-stage renal disease in children and adults (31). Autosomal dominant polycystic kidney disease (ADPKD) occurs in 1:1,000 individuals, primarily as the result of mutations in one of two genes, *PKD1* or *PKD2* (81, 150–152). In comparison, autosomal recessive polycystic kidney disease (ARPKD) is much less frequent (1:20,000 live births) and results primarily from mutations in a single gene, *PKHD1* (107, 162).

The principal pathological manifestations in PKD involve *1*) the formation of epithelial-lined cysts throughout the nephron in ADPKD and predominantly in the collecting duct in ARPKD; *2*) alterations in cell polarity; and *3*) changes in extracellular matrix composition. In addition to the renal cystic disease, ADPKD is associated with cyst formation in other epithelial organs, most notably the liver and pancreas, as well as connective tissue defects, such as intracranial aneurysms, aortic dissection, cardiac valve abnormalities, and abdominal wall hernias (116). In comparison, the ARPKD phenotype is expressed almost exclusively in the kidney and liver, with the latter lesion involving biliary dysgenesis and portal tract fibrosis (20).

Efforts to elucidate the mechanisms that underlie PKD pathogenesis have been greatly enhanced by studies in experimental systems, most notably murine (mouse and rat) models of PKD. Numerous mouse and rat PKD models have been described in which the mutant phenotypes closely resemble human PKD with respect to cyst morphology, cyst localization, and disease progression (reviewed in Refs. 48 and 135). Some of these models are the result of spontaneous mutations, whereas others were engineered through chemical mutagenesis, transgenic technologies, or gene-specific targeting in mouse orthologs of human PKD genes.

These murine models share common pathogenic features with human PKD. These include *1*) dysregulated epithelial cell proliferation and differentiation; *2*) alterations of tubular basement membrane constituents and the associated extracellular matrix; *3*) abnormalities of epithelial cell polarity with apical mislocalization of key receptors and enzymes; and *4*) abnormalities in transepithelial fluid transport (reviewed in Ref. 13). These parallel observations in murine models and human PKD prompt the hypothesis that mammalian PKD genes may define common molecular pathways that are involved in cystogenesis and PKD progression.

This review examines murine PKD models that are transmitted as single-gene disorders. It highlights the most widely studied models; discusses how investigations in these models have advanced our understanding of PKD pathogenesis; and examines the effect of various therapeutic interventions in these PKD models. Experimental systems induced by transgenesis and chemical modulation are not discussed, and the reader is referred to several excellent reviews (35, 48, 135).

MOUSE PKD MODELS

In the mouse, PKD is generally transmitted as an autosomal recessive trait (Table 1). Several of these models resemble human ARPKD with respect to renal cyst pathology and disease progression. Other models,

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Table 1. *Murine models of polycystic kidney disease*

Model	Transmission	Gene	Protein	Human PKD Phenocopy†*	Left-Right Axis Defect	Cilia Expression‡
			Mouse			
cpk	AR	*Cys1*	Cystin	ARPKD	No	Yes
bpk	AR	*Bicc1*	Bicaudal C	ARPKD	No	Yes§
jcpk	AD/AR	*Bicc1*	Bicaudal C	ADPKD	No	Yes§
orpk	AR	*TgN737Rpw*	Polaris	ARPKD	Yes†	Yes
inv	AR	*Invs*	Inversin	ARPKD	Yes	Yes
jck	AR	*Nek8*	Nek8	ADPKD	No	NE
kat	AR	*Nek1*	Nek1	ADPKD	No	NE
pcy	AR	NI	NI	ADPKD	No	NI
			Rat			
Han:SPRD-cy	AD/AR	NI	NI	ADPKD	No	NI
wpk	AR	NI	NI	ARPKD	No	NI
pck	AR	*Pkhd1*	Fibrocystin	ARPKD	No	NE

PKD, polycystic kidney disease; *cpk*, congenital polycystic kidneys; *bpk,* BALB/c polycystic kidneys; *jcpk,* juvenile congenital polycystic kidney; *orpk,* Oak Ridge polycystic kidney; *inv,* inversion of embryonic turning; *jck,* juvenile cystic kidney; *kat*, kidney, anemia, testis; *pcy,* polycystic kidney disease; *wpk*, Wistar polycystic kidneys; *pck,* polycystic kidneys; AR, autosomal receive; AD, autosomal dominant; NE, not yet evaluated; NI, gene not yet identified. *Kidney phenotype. †Homozygosity for null allele (embryonic lethal). ‡Cilia expression. §Guay-Woodford, unpublished observations.

with cysts distributed along the entire nephron, extrarenal manifestations, and slower disease progression, more closely approximate the human ADPKD phenotype.

Models Arising From Spontaneous Mutations

The congenital polycystic kidneys (*cpk*) mutation arose spontaneously in the C57BL/6J (B6) strain. The *cpk* model was the first to be described (30, 118), and as such it is probably the most extensively characterized. Mutants develop massive renal cystic disease and progressive renal insufficiency in a pattern that strongly resembles human ARPKD. Initial cystic changes are evident at approximately embryonic *day 16* (*E16*) and are localized primarily to the proximal tubule (4, 33). With progressive postnatal age, the cystic change transitions to predominantly collecting duct involvement. Death occurs by 3–4 wk of age, presumably due to uremia.

Both disease expression and severity are modulated by genetic background (50, 171). The ductal plate malformation (DPM), the biliary abnormality described in human ARPKD, is not penetrant in B6-*cpk*/*cpk* mice (30). However, when *cpk* is expressed on other genetic backgrounds, e.g., *Mus mus castaneus* (CAST/Ei), DBA/2J, BALB/c, or CD1, *cpk* mutants have renal collecting duct cysts as well as biliary and pancreatic duct abnormalities (38, 40, 50, 125). B6 heterozygotes do not express disease, whereas aged F1 heterozygotes from crosses with the DBA/2J and BALB/c strains can develop biliary cysts.

The *cpk* locus maps to mouse chromosome (Chr) 12 (138). *Cys1*, the *cpk* gene, was recently identified by positional cloning (56). It is predicted to encode a novel, hydrophilic, 145-amino acid protein (cystin) that has no significant similarity to previously characterized proteins or protein domains. However, cystin has two potential myristoylation sites, the more NH_2 terminal of which is coupled to a polybasic domain. Proteins with such NH_2-terminal myristoylation motifs are typically associated with intracellular membranes (79). Expression studies in mouse collecting duct cells have demonstrated that cystin localizes to the primary apical cilia, perhaps with the ciliary axonemal membrane (56, 176).

The *cpk* allele involves a tandem deletion that causes a frameshift within exon 1 and a premature termination shortly thereafter. The truncated protein is predicted to be nonfunctional.

The BALB/c polycystic kidneys (*bpk*) mutation arose spontaneously on the BALB/c inbred background. Like *cpk*, the *bpk* mutation is transmitted as a fully penetrant, recessive trait (95). Affected homozygotes develop both cystic dilatation of the renal collecting ducts as well as biliary dysgenesis, and the genetic background modulates disease progression. Death ensues within 4 wk of birth, presumably due to renal insufficiency.

The mutant locus maps to mouse Chr 10 (49) and, in a somewhat surprising result, complementation testing has indicated that *bpk* is allelic with *jcpk*, a PKD mutation that has more phenotypic similarity to ADPKD. Recent studies have demonstrated that the mouse bicaudal C gene (*Bicc1*) is disrupted in the *bpk* and *jcpk* models (15). *Bicc1* encodes two splice variants, *transcript A* and *transcript B*, and both are expressed in the kidney. The predicted protein from *transcript A* contains three NH_2-terminal K homology (KH) motifs and a COOH-terminal sterile α motif (SAM) domain, whereas *transcript B* is shorter with an altered SAM domain. Studies in *Drosophila* (131) indicate that the KH domains mediate protein-RNA interactions in which bicaudal C acts as a critical translational regulator in oogenesis. The function of the SAM domain is less well studied but is proposed to be involved in protein-protein interactions (136).

The *bpk* mutation, involving a 2-bp insertion in exon 22, is not predicted to disrupt *transcript B*. *Transcript*

A from the *bpk* allele would encode intact KH and SAM domains, but the insertion would cause a dramatic elongation of translated protein. In comparison, the *jcpk* allele involves a 1-bp change in the consensus splice acceptor site for exon 3, resulting in a frameshift that causes a premature termination shortly thereafter. Thus the resulting protein does not contain any KH domains or the SAM domain and is predicted to be nonfunctional.

The inversion of embryonic turning (*inv*) mutation occurred in the OVE210 transgenic line due to a random insertional event of the tyrosinase minigene. Mutants express a complex recessive trait characterized by complete reversal of embryonic left-right body axis determination (situs inversus), renal and pancreatic cysts, and anomalous development of the extrahepatic biliary system. While the renal cystic disease resembles human ARPKD, the biliary lesion causes an early onset cholestatic jaundice. Death typically occurs within the first week of life.

Transgene integration at the *inv* locus caused a 47-kb deletion that disrupts *Invs*, the gene encoding inversin, a novel protein that contains ankyrin repeats and calmodulin-binding motifs (80, 83). Recent studies have identified at least three inversin isoforms, which localize to different subcellular compartments, including the nucleus cell-cell adhesion sites (97), as well as the primary apical cilia (82). The data suggest that inversin isoforms may function in similar cellular processes as β-catenin, including intercellular junction biogenesis and transcriptional regulation.

The *inv* locus maps to Chr 4. The human syntenic interval on chr 9q22–31 contains *NPHP2*, the disease-susceptibility locus for an early onset, rapidly progressive form of nephronophthisis (NPH) (52). Recent studies in NPHP2 patients have identified mutations in human *INVS* (110a).

The juvenile cystic kidney (*jck*) mutation occurred in a line of mice carrying the MMTV/c-myc transgene (1). Subsequent studies demonstrated that the *jck* locus and the transgene segregated separately, and thus the mutational event was independent of the transgene. In affected mice, focal renal cysts are evident as early as 3 days of life and the renal cystic disease is slowly progressive. Mutants are fertile and generally survive 4 mo or more. The severity of renal cystic disease is modulated by genetic background, and two major modifying loci have been identified (57). No histological abnormalities in other organs have been described.

The *jck* locus maps to Chr 11. The mutant allele has a missense change in *Nek8*, encoding the NIMA (for never in mitosis A)-related kinase 8 (71). To confirm that a *Nek8* defect causes renal cysts, cross-species analysis was performed, using morpholino anti-sense oligonucleotides directed against the zebrafish *Nek8* ortholog. Morpholino-injected zebrafish embryos developed a PKD-like phenotype with cystic change in their kidney equivalent, the pronephric duct.

The kidney, anemia, testes (*kat*) mutation arose spontaneously in the inbred RBF/Dn strain and second mutant allele, kat^{2J}, occurred independently in the C57BL/6J strain (60). The kat^{2J} allele is associated with more rapidly progressive disease, but both *kat* and kat^{2J} homozygotes express a fully penetrant, pleotropic phenotype that includes polycystic kidney disease, facial dysmorphism, dwarfing, male sterility, anemia, and choroid plexus cysts (60, 160). The renal cystic lesion is first evident at approximately 2 mo of age, with cysts expressed primarily in Bowman's space and proximal tubules. Disease progression occurs over months and is strongly influenced by genetic background (160). Mutants die prematurely, probably due to the combined effects of renal failure, anemia, and hydrocephalus. Given its latent disease onset, systemic manifestations, and slow progression to renal failure, the *kat* mouse has been proposed as a model for the study of human ADPKD.

The mutant locus maps to mouse Chr 8. Upadhya et al. (159) have demonstrated that the *Nek1* gene, encoding the NIMA-related kinase 1, is disrupted by both mutations. The *kat* allele involves a 1.3-kb intragenic deletion, whereas the kat^{2J} allele results from a single bp insertion. Both changes occur within the kinase domain. The resulting frameshifts lead to premature stop codons, with protein products predicted to lack the entire COOH-terminal tail.

The polycystic kidney disease (*pcy*) mutation first occurred on the diabetic-prone KK mouse strain (145, 146). The initial phenotype resembled human ADPKD with respect to renal cyst localization and slow disease progression. Subsequently, the mutant locus was transferred to the DBA/2J strain and transmitted as a fully penetrant, autosomal recessive trait. Segmental dilatation of distal tubules is initially observed in newborn mutants. Renal cysts gradually extend to all nephron segments and progressively enlarge. Mutants develop renal enlargement after 8 wk of age, with progressive azotemia and interstitial fibrosis by 18 wk of age. Death due to renal failure occurs between 30 and 36 wk of age. Renal disease progression is modulated by genetic background, and two major modifying loci have been identified (172). Although most mutants do not express extrarenal manifestations, a few develop cerebral vascular aneurysms in the late stages of the disease.

Given the slowly progressive nature of the renal cystic disease and the occasional occurrence of cerebral aneurysms, the *pcy* mouse has been widely viewed as a model for human ADPKD. Its cellular and molecular defects have been extensively characterized, and numerous therapeutic interventions have been evaluated in this model (see MURINE MODELS AND POTENTIAL TARGETS FOR PKD TREATMENT).

The *pcy* locus maps to mouse Chr 9 (88). This interval is syntenic with a region on human chr 3q21–22 that contains the locus for *NPHP3*, a late-onset disorder of the NPH/medullary cystic kidney disease (NPH/MCD) complex (106). These genetic studies, when coupled with histopathological analysis of *pcy* kidneys, suggest that the *pcy* mouse may be a more appropriate model for the human NPH/MCD complex than ADPKD.

Finally, two other mouse cystic kidney disease models deserve mention. While neither is presently the focus of intensive investigation and the disease-susceptibility genes have yet to be identified, each model suggests a potential interplay between the immune system and the development and/or the progression of cystic kidney disease.

The *CFWwd* mutation occurred spontaneously in the CFW substrain of the AKR inbred line (165). Mutants develop a form of cystic kidney disease that resembles human ADPKD with respect to renal cyst morphology and the expression of extrarenal manifestations, including hepatic cysts and thoracic aortic aneurysms. Genetic studies suggest an autosomal dominant mode of transmission, but penetrance is strongly influenced by environmental exposure. When raised in a conventional facility, 100% *CFWwd* mice develop disease, compared with only 4% of *CFWwd* mice raised in a germ-free environment. The disease-susceptibility gene has yet to be identified, and the putative gene-by-environment interactions have not been defined.

The kidney disease (*kd*) mutation arose spontaneously in the CBA/CaH inbred mouse strain and is transmitted as a fully penetrant, recessive trait (75). CBA/CaH-*kd*/*kd* mice develop a progressive, T cell-mediated, autoimmune interstitial nephritis and die at 5–7 mo with inanition, a urinary concentrating defect, and uremia. The characteristic histopathological lesion develops in the renal cortex between 10 and 14 wk of age and consists of cystic tubular dilatation with focal peritubular mononuclear cell infiltrates (139). Given the similarities in renal histopathology, the *kd* mouse has been proposed as a model for the NPH/MCD complex of disorders (75). The *kd* locus maps to Chr 10 in tight linkage with *Col13a1*, the gene encoding the α_1 chain of collagen XIII (21). Recombination mapping studies have excluded *Col13a1* as a candidate *kd* gene (85).

PKD Models Engineered Through Chemical Induction or Insertional Mutagenesis

The juvenile congenital polycystic kidney (*jcpk*) mutation was recovered in a chlorambucil mutagenesis program (28). Homozygous *jcpk* mice die before 10 days of age and have numerous cysts in all nephron segments, from the glomerulus to the collecting ducts. The liver and pancreas are also affected, with large dilatations of the intrahepatic biliary ductules and pancreatic ductules. Approximately 30% of heterozygous +/*jcpk* mice also develop a late-onset renal cystic disease that involves only the glomeruli.

As noted above, the *jcpk* mutation disrupts the *Bicc1* gene, resulting in a markedly truncated protein that is predicted to be nonfunctional (15).

The Oak Ridge polycystic kidney (*orpk*) mutation was recovered from large-scale insertional mutagenesis program (84). The specific mutant line, *TgN737Rpw*, was generated by pronuclear injection of a reporter transgene into FVB/N oocytes. The mutant phenotype is transmitted as an autosomal recessive trait and characterized by severe growth retardation, PKD, intrahepatic biliary DPM, and pancreatic ductal hypoplasia (84, 178), as well as skeletal patterning defects, including craniofacial abnormalities, cleft palate, supernumerary teeth, and preaxial duplication of digit one (180). On *day 1* of life, the renal cystic disease is primarily expressed in the proximal tubules, but by postnatal *day 7*, collecting duct dilatation predominates (84). This pattern of early proximal tubule dilatation followed by a shift to predominantly collecting duct dilatation has also been described in the *cpk* (4), and *bpk* (95) models, as well as in human ARPKD (92). In *orpk* mutants, inanition and renal failure evolve rapidly, with death in the first 1–2 wk of life. However, genetic background significantly modulates disease severity and mortality (140).

The novel gene interrupted by the transgene insertion encodes polaris, a protein containing 10 copies of an internally repeated, 34-amino acid tetratricopeptide repeat (84). The wild-type allele encodes a predominant 3.2-kb transcript as well as two larger transcripts of lower abundance. Expression of the predominant transcript as a transgene (Tg737Bap) in *orpk* mutants differentially rescued the renal lesion (177).

Further genetic analyses determined that $Tg737^{orpk}$ is a hypomorphic allele (84, 149, 178) and a second targeted mutation, $Tg737^{\Delta 2\text{-}3\beta Gal}$, represents a null allele (86). Homozygous $Tg737^{\Delta 2\text{-}3\beta Gal}$ embryos die in early to midgestation, with randomization of left-right axis specification, failure of neural tube closure, and limb patterning defects (86). The data indicate that polaris plays a critical role in embryonic patterning and development.

Targeted Mutagenesis of Human PKD Orthologs

The identification of the human ADPKD genes, *PKD1* and *PKD2*, prompted the characterization and targeted mutagenesis of their mouse orthologs, *Pkd1* and *Pkd2* (summarized in Tables 2 and 3). Both null and hypomorphic alleles ($Pkd1^{del34}$; $Pkd1^{L}$; $Pkd1^{del17\text{-}21\beta geo}$; $Pkd1^{m1Bei}$) have been generated (8, 11, 54, 65, 73, 74, 87, 115, 173). Heterozygous mice develop renal, biliary, and pancreatic cysts between 4 and 19 mo of age. Homozygous mutants develop renal and pancreatic cysts at *E15.5*, coincident with the induction of *Pkd1* and *Pkd2* expression in normal maturing tubular epithelia (11). In addition, cardiac septation defects, vascular fragility, fetal hydrops, and skeletal anomalies have also been observed in some targeted models. Disease progression is rapid, with embryonic lethality occurring in most homozygous mutants. These data, demonstrating that loss of *Pkd1* or *Pkd2* is sufficient to cause renal cysts, support the two-hit model of cystogenesis proposed for ADPKD.

Additional evidence is provided by mice carrying the $Pkd2^{WS25}$ allele (173). This allele can encode wild-type polycystin-2 protein but is prone to somatic genomic rearrangement, resulting in a null allele. Renal cysts develop in 53% of $Pkd2^{WS25/WS25}$ vs. 100% of mice heterozygous for the $Pkd2^{WS25}$ allele and a *Pkd2* null

Table 2. *Targeted mutations in mouse Pkd1*

Strain/(Ref. No.)	Mutation	Allele*	*Pkd1*$^{-/-}$	Visceral Organ Cysts	Cardiovascular Defects	Edema	Skeletal Defects	*Pkd1*$^{+/-}$
Pkd1^{del34} (62)	Exon 34 deletion	*Pkd1*^{tm1Jzh}	EL	Kidney, pancreas	NE	+	+	Kidney, liver, pancreas cysts
Pkd1^{null} (63)	Exon 4 disruption	*Pkd1*^{tm2Jzh}	EL	Kidney, pancreas	NE	+	+	Kidney, liver, pancreas cysts
Pkd1^{L} (64)	Exon 43–45 deletion	*Pkd1*^{tm1Maa}	EL	Kidney, pancreas	Vascular leak	+	No data	No data
Pkd1$^{del17\text{-}21\beta geo}$ (65)	Exon 17–21 deletion; IRES lacZ-neo fusion	*Pkd1*^{tm1Rsa}	EL	Kidney	Conotruncal defects	+	+	Kidney, liver cysts
Pkd1^{-} (66)	Exon 2–4 deletion with in-frame lacZ	*Pkd1*^{tm1Shh}	EL	Kidney, pancreas	No data	No data	No data	No data
Pkd1^{-} (67)	Exon 2–6 deletion	NA	EL	Kidney	Conotruncal defects	+	No data	No data
Pkd1^{-} (72)	Exon 1 disruption	NA	EL	Kidney, pancreas	NE	+	No data	Kidney, liver cysts
Pkd1^{-} (68)	Point change due to ENU mutagenesis	*Pkd1*^{m1Bei}	EL	Kidney	No data	No data	No data	Kidney, liver, pancreas cysts

Pkd1$^{-/-}$, homozygous for the targeted mutation; *Pkd1*$^{+/-}$, heterozygous for the targeted mutation; EL, embryonic lethal, with death between embryonic *day 15.5* and birth; ENU, *N*-ethyl-nitrosourea; +, present; NA, not assigned. *Assignment in the Mouse Locus Catalogue (www.informatics.jax.org/searches/alleles).

allele (*Pkd2*$^{WS25/-}$). Immunohistochemical analyses revealed staining for polycystin-2 in normal, but not cystic, tubular epithelium, indicating that the *Pkd2* gene is inactivated in cystic epithelial cells.

While the two-hit hypothesis is consistent with the phenotypes in *Pkd1*- and *Pkd2*-targeted models, other data suggest that additional genetic mechanisms may be in play. For example, mice overexpressing a human *PKD1* transgene develop an ADPKD-like renal and biliary cystic disease (119). In addition, data from *Pkd1*$^{-/+}$:*Pkd2*$^{-/+}$ *trans*-heterozygous mice suggest that haploinsufficiency may play a role in cystogenesis. These mice exhibit more severe renal disease than would be predicted by a simple additive effect from each single mutation (174). Taken together, these results indicate that a complex set of mechanisms, including somatic inactivation, overexpression, and haploinsufficiency of *Pkd1* and/or *Pkd2*, may play roles in ADPKD pathogenesis.

RAT PKD MODELS

Compared with the mouse, where different genetic mechanisms have given rise to a large number of PKD models, only a few heritable rat PKD models have been described, and all result from naturally occurring spontaneous mutations (Table 1).

The Han:SPRD-*cy* rat is well characterized and has been studied extensively as a model of ADPKD (17, 48, 61, 134). The mutation arose spontaneously in the Sprague-Dawley strain, and initial analysis indicated inheritance as an autosomal dominant trait. In heterozygotes, the renal cystic lesion is evident within the first few weeks of life, primarily involves the proximal tubules, and progresses slowly. There is sexual dimorphism in disease expression. Renal enlargement and cystic change evolve more rapidly and interstitial fibrosis is more pronounced in male *Cy*/+ rats than in age-matched female heterozygotes (19, 47). Azotemia

Table 3. *Targeted mutations in mouse Pkd2*

Strain/(Ref. No.)	Mutation	Allele*	*Pkd2*$^{-/-}$	Left-Right Axis	Visceral Organ Cysts	Cardiovascular Defects	Edema	Skeletal Defects
Pkd2^{-} (69)	Exon 1 disruption	*Pkd1*^{tm1Som}	EL	No data	Kidney, pancreas	+	+	No data
Pkd2^{WS25} (69)	Exon 1 duplication generating unstable allele	*Pkd1*^{tm2Som}	Viable	No data	Kidney, liver, pancreas	NE	NE	No data
Pkd2^{-LacZ} (70)	Exon 1 deletion *LacZ* "promoter trap"	NA	EL	Randomization; right pulmonary isomerism	Kidney, pancreas	+	+	No data

Pkd2$^{-/-}$, homozygous for the targeted mutation. *Assignment in the Mouse Locus Catalogue (www.informatics.jax.org/searches/alleles).

develops by 8 wk of age in *Cy*/+ males, but renal function declines slowly and male heterozygotes routinely live into the second year of life. Female heterozygotes appear to have a normal life span.

The *cy* allele exhibits a gene-dose effect, as *cy*/*cy* homozygotes develop a rapidly progressive form of PKD, with massive renal enlargement, rapid-onset azotemia, and death by 3 wk of age. Cystic changes involve all nephron segments (17, 134).

Based on the autosomal dominant mode of transmission, the slowly progressive nature of the renal cystic disease, and its differential severity in male heterozygotes, the Han:SPRD *Cy*/+ rat has been long considered as a model for human ADPKD. The cellular and molecular defects in *Cy*/+ kidneys have been extensively characterized, and numerous therapeutic interventions have been evaluated in this model (see MURINE MODELS AND POTENTIAL TARGETS FOR PKD TREATMENT). However, it is important to note that unlike human ADPKD, the renal cystic lesion in the Han:SPRD *Cy*/+ rat is confined primarily to proximal tubule segments, and there are virtually no extrarenal manifestations in this model.

The Han:SPRD-*cy* locus, *Pkdr1*, maps to rat Chr 5 (9). In both sexes, renal cystic disease is modulated by genetic background. Genetic mapping studies have identified a rat Chr 8 locus designated *Modpkdr1*, which exerts a main effect on renal disease severity (10).

The Wistar polycystic kidneys (*wpk*) mutation arose spontaneously in an outbred Wistar strain (94). Homozygous mutants develop nephromegaly, hypertension, proteinuria, impaired urinary concentrating capacity, and uremia, resulting in death at 4 wk of age. Cysts initially develop at *E19*. Lectin-binding studies and electron microscopy have identified cystic changes in proximal tubules, thick limbs, distal tubules, and collecting ducts. With progressive postnatal age, the cystic change shifts to predominantly involve the collecting ducts. While *wpk* mutants exhibit renal histopathology that is strikingly similar to human ARPKD, the biliary ductal plate malformation invariably associated with the human disease is not evident.

The *wpk* locus maps just proximal to the Han:SPRD-*cy* locus on rat Chr 5, but complementation studies have demonstrated that these loci are not allelic (94). Comparative homology mapping indicates that the mouse and human *wpk* orthologs are not allelic with any previously described mouse PKD model or human PKD gene.

The polycystic kidneys (*pck*) mutation developed spontaneously in the Crj:CD/SD strain and is transmitted as an autosomal recessive trait (68). In affected homozygotes, the renal architecture is normal at birth. Renal cystic lesion appears after the first week of life, with cysts expressed primarily in the thick ascending loops of Henle, distal tubules, and collecting ducts. The renal disease is characterized by progressive cystic changes, with focal interstitial inflammation and fibrosis developing by 70 days of age. Biliary ductal dilatation is evident as early as 1 day of age, progresses with age, and is associated with marked hepatomegaly, but minimal portal tract fibrosis. There is a mild sexual dimorphism in renal cystic disease expression, with males more severely affected than females.

Given the late-onset and slowly progressive PKD, the *pck* rat was initially proposed as a model of human ADPKD (68). However, subsequent genetic mapping positioned the *pck* locus on rat Chr 9, in a narrow region of synteny with human chr 6p. This interval included the human ARPKD locus. Comparative genomic studies led to the identification of the human ARPKD gene, *PKHD1*, and confirmed that the rat ortholog, *Pkhd1*, was disrupted in the *pck* model (162). These studies represent the first demonstration that orthologous genes are involved in human PKD and a spontaneously occurring murine PKD model.

One additional rat PKD model should be mentioned. The Wistar-*chi* or rat ARPK model was described more than 10 years ago (59, 104). In this autosomal recessive trait, the phenotype is characterized by growth retardation, polycystic kidneys, and abnormalities of the cranium, limbs, and axial skeleton. The renal cystic lesion is expressed primarily in collecting ducts, in a pattern similar to that in human ARPKD. However, the renal insufficiency progresses slowly, and death, presumably due to uremia, occurs between 6 and 11 mo of age.

QUANTITATIVE TRAIT LOCI AND PKD PATHOGENESIS

PKD is a Complex Trait

Disease expression is quite variable among human PKD families as well as in murine experimental models. Several possible mechanisms may contribute to this variability, including *1*) mutations in different disease-susceptibility genes; *2*) different mutant alleles of the same disease gene; *3*) random somatic events that disrupt the wild-type allele, e.g., in ADPKD; and *4*) modifying influences such as gene-gene or gene-environment interactions.

Among individuals with defects in the same PKD gene, the limited genotype-phenotype analyses conducted to date reveal minimal correlation between mutant alleles and clinical phenotypes (7, 76, 130). Moreover, within human families and experimental crosses segregating specific mutant alleles, disease phenotypes can vary widely. These data are consistent with observations in numerous other single-gene disorders. Dipple and McCabe (24) have therefore proposed that in single-gene disorders, the primary mutant gene product is embedded in a highly complex system that includes other, independent genetic variations (genetic modifiers) and modulating environmental factors. In other words, the phenotypes in single-gene disorders, including PKD, are in fact complex traits.

The molecular interactions of PKD-susceptibility genes and their putative genetic modifiers are likely to define critical pathways critical for cystogenesis and PKD progression. The characterization of these genetic pathways should provide new insights into disease pathogenesis, identify genetic markers for prognosis, and establish a molecular platform from which to de-

velop targeted therapeutic interventions to slow disease progression.

Genetic Dissection of Complex Traits

The genetic pathways involved in complex traits can be examined more efficiently in experimental models than in natural populations, such as human families (179). In experimental crosses, genetic modifying effects can be dissected into discrete factors referred to as quantitative trait loci (QTL) (127). Using genome-scanning strategies, QTL are first localized to a specific genetic interval. Special "congenic" strains are then constructed to isolate the disease-modulating interval from one parental strain on the genetic background of the other parental strain. Systematic refinement of the congenic interval then facilitates QTL isolation and characterization (67). The interaction between the mutant allele and the QTL can then be examined to determine the cellular function of disease-susceptibility genes and to elucidate the pathways in which they operate (58). Therefore, by identifying genetic variants in complex developmental pathways, QTL mapping provides a strategy for investigating the biology of complex physiological traits (111), such as PKD.

QTL Mapping in Murine PKD Models

In each of the murine models described, genetic background appears to modulate the renal cystic phenotype. In these models, putative modifying effects have been dissected into discrete QTL and genetically mapped (summarized in Table 4).

Several lines of experimental evidence support the hypothesis that PKD genes and their modifiers may define pathways involved in cystogenesis and PKD progression. First, the same QTL interval on Chr 1 exerts effects on renal disease severity in the *jck* and *kat* models (57, 160). Second, an interval on proximal Chr 4 contains putative modifying gene(s) for the *cpk*, *bpk, jck,* and *pcy* models (51, 67, 171, 172). The *inv* locus maps within this Chr 4 interval, suggesting that non-PKD-causing *Invs* alleles may modulate renal cystic disease severity in other PKD models. Similarly, QTL mapping data suggest that the *Bicc1* gene disrupted by the *bpk* and *jcpk* mutations may also be a candidate PKD-modifying gene. A speculative model proposes there are at least four alleles at this locus (49). Homozygosity for either the *bpk* or *jcpk* allele causes PKD. By itself, the D2 allele does not cause any kidney defect. However, when this allele is expressed together with mutations at the unlinked *jck* locus, the cystic kidney lesion is exacerbated. Finally, the B6 allele appears to act as a wild-type allele and is not associated with any defect.

In the Han:SPRD-*cy* rat, QTL mapping has suggested a candidate PKD QTL on rat Chr 8. Comparative genomic analysis indicates that this interval is conserved on mouse Chr 9 and the syntenic region contains a candidate QTL involved in progressive renal disease in the *Col4a3*$^{-/-}$ mouse model of Alport syndrome, a hereditary glomerular disorder. In addition, there is suggestive evidence for a second QTL more distal on Chr 8 that has syntenic conservation with the *pcy* interval on mouse Chr 9 and the interval on human chr 3q22 that contains *NPHP3,* the locus involved in an adolescent form of NPH.

Taken together, these mapping data are permissive for the hypothesis that the molecular interactions of PKD-susceptibility genes and their genetic modifiers define pathways that modulate PKD-related disease progression. Different allelic variants of a given gene may cause PKD, modulate PKD, or exert no detrimental effect. With the recent identification of several PKD genes, it is now feasible to design direct analyses to test this hypothesis.

Table 4. *Quantitative trait loci underlying kidney disease severity*

Model	Cross	QTL Interval	cM	LOD score
		Mouse		
bpk	BALB × CAST	*D6Mit14*	63	5.5
		D1Mit117	110	2.1
cpk	B6 × CAST	*D4Mit111*	25	10
jck	B6 × D2	*D1Mit7*	42	16.8
		D4Mit286	19	5.2
		D10Mit14	70	2.1
kat	B6 × CAST	*D1Mit8*	51	6.0
		D19Mit11	28	2.6
orpk	FVB/N × C3H	*D4Mit134*	62	2.2
pcy	D2 × CAST	*D4Mit111*	25	10
		D16Mit1	18	14
		Rat		
Han:SPRD-cy	SPRD × BN	*D8Rat17*		2.1*

Mouse strains: BALB, BALB/c; CAST, CAST/Ei; B6, C57BL/6J; D2, DBA/2J. Rat strains: SPRD, Sprague-Dawley; BN, Brown Norway. QTL, qualitative trait loci; cM, centimorgan; LOD score, likelihood of odds score. *Original data (10) reported as *F*-statistic = 9.834. For analyses with 1 df, the *F*-statistic can be converted to a LOD score by the formula LOD = 0.217 × *F*.

PKD PATHOGENESIS: ROLE OF THE PRIMARY APICAL CILIA

Multiple cellular and extracellular matrix abnormalities have been described in different murine PKD models. However, recent studies have provided a provocative and entirely unexpected insight; that is, structural and/or functional defects in the primary apical cilia of tubular epithelia may play a role in PKD pathogenesis.

The Primary Apical Cilia and PKD Pathogenesis

Primary cilia are hairlike structures that emerge typically as single projections from one of the two basal bodies (centrioles) (166, 167). Typical cross-sectional schemas depict the cilia membrane surrounding a central core or axoneme consisting of microtubules arranged in nine peripheral bundles (9+0 pattern) (Fig. 1). However, detailed ultrastructural studies in renal epithelia have demonstrated that the axonemal structure actually varies along the cilia length, with the 9+0 pattern near the base, an 8+1 or 7+2 pattern in the

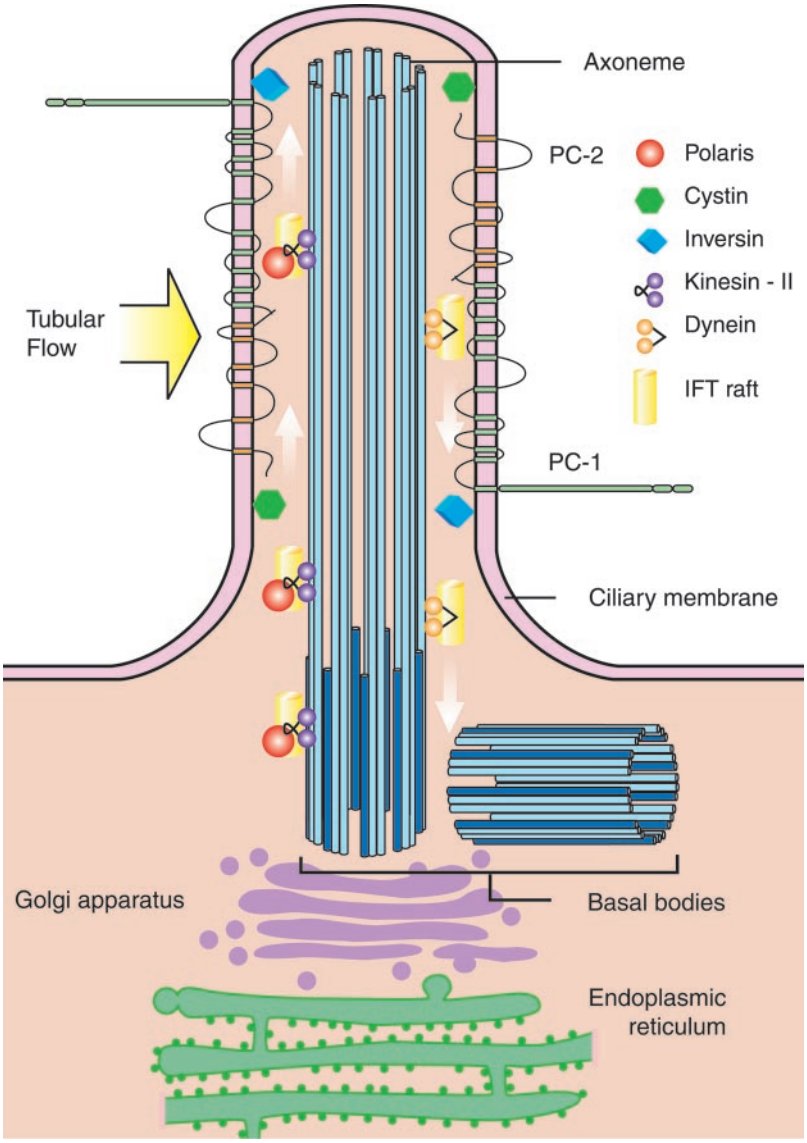

Fig. 1. The primary apical cilium in renal epithelia. Primary cilia are hairlike structures that emerge from 1 of the 2 basal bodies (centrioles) just below the apical membrane. The basal bodies are oriented perpendicular to one another, and each contain 9 microtubule triplets. The ciliary axoneme extends from the basal body and consists of microtubules arranged as 9 peripheral doublets (9+0 pattern). Along this axonemal scaffold, large protein complexes [intraflagellar transport (IFT) rafts] are transported in a bidirectional fashion. Antegrade or outward movement of IFT rafts is powered by the kinesin-II molecular motor [heterotrimeric kinesin (KIF3)], whereas the retrograde or inward movement is dependent on cytoplasmic dynein 1b/2 (reviewed in Ref. 129). Polaris, the protein disrupted in *orpk* mice, is an IFT raft component thought to play a critical role in ciliogenesis. Cystin, the protein truncated in *cpk* mice, is proposed to be associated with the ciliary membrane. The *Invs* protein product inversin is localized to cilia, but its intraorganelle associations remain to be defined. Both polycystin-1 (PC-1) and polycystin-2 (PC-2) localize to the primary cilia and are proposed to function in a mechanotransduction pathway.

midaxoneme, and a more irregular pattern near the tip, where doublets often reduced to single microtubules (29, 164). Cilia with the 9+0 configuration are generally immotile, with the exception of embryonic nodal cilia that beat in a rotational fashion and direct embryonic left-right patterning (96). In comparison, the axonemes of motile cilia, such as those expressed in multiple copies on epithelia of the respiratory tract, the ventricular ependymal layer, the oviduct and the efferent duct, consist of nine peripheral bundles connected by dynein arms and two central microtubules (9+2 pattern).

In renal tubular epithelia, one (rarely 2) primary cilium projects from the apical membrane of every cell type, except intercalated cells (166). Indeed, primary cilia have been observed in most cells in the body, including both ductal and nonductal epithelial cells, endothelia, neurons, mesenchymal cells, fibroblasts, chondrocytes, and osteocytes (29, 166, 167). These primary cilia have long been considered to be vestigial organelles. However, recent data indicate that, in addition to their role in left-right embryonic patterning, primary cilia function as mechanosensors (renal tubular epithelia) (93, 117), photosensors (retinal pigmented epithelia) (113), and chemosensors (olfactory neurons) (112).

A role for the primary apical cilia in PKD pathogenesis has been suggested by studies in the *orpk, cpk*, and *inv* mouse models. In each case, the disease-susceptibility gene encodes a cilia-associated protein. Polaris, the protein disrupted in *orpk* mutants, localizes to the ciliary axoneme and the basal bodies (149). Mice homozygous for the $Tg737^{orpk}$ allele express an ARPKD phenotype with severe stunting of the primary apical cilia in renal, biliary, and pancreatic epithelia, as well as in the ventricular ependymal epithelia (149). In comparison, the embryonic ventral nodal cells of $Tg737^{\Delta 2\text{-}3\beta Gal}$ mutants do not express cilia, resulting in randomization of left-right body axis determination and embryonic lethality (86). Expression of a Tg737 transgene

rescues the lethal phenotype as well as the laterality defects in *Tg737*$^{\Delta 2-3\beta Gal}$ mutant embryos and delays cystogenesis in both the *Tg737*$^{\Delta 2\text{-}3\beta Gal}$ and *Tg737*^{orpk} mutants (12).

Similar to the *orpk* model, *inv* mutants express left-right patterning defects and an ARPKD-like phenotype (80, 83). Several isoforms of inversin have been described and within renal tubular epithelia, these isoforms are distributed to the primary apical cilia (82), cell-cell adhesion sites, and the nucleus (97; Phillips C, personal communication). Transgenic reexpression of at least one isoform rescues the embryonic laterality defect as well as the renal cystic phenotype in *inv* mutants (163).

Further evidence of a link between laterality defects and PKD is provided by two recent targeted models. In the *Pkd2*$^{-LacZ}$ mouse, a targeted deletion of exon 1 was generated using a *LacZ* "promoter trap" (115). Homozygotes have randomization of left-right patterning, right pulmonary isomerism, and dextrocardia as well as renal and pancreatic cysts. Death occurs before birth. Similarly, homozygosity for a targeted disruption of *Kif3a*, the gene encoding KIF3A, a subunit of the cilia molecular motor kinesin-II, results in abnormalities of left-right axis determination and embryonic lethality. However, mutants with tissue-specific inactivation of *Kif3a* in renal tubular epithelia cells are viable. At birth, the kidneys are structurally normal. Cysts begin to develop at postnatal *day 5* with rapid progression to renal failure by postnatal *day 21*. The cystic epithelial cells lack primary cilia and exhibit increased proliferation and apoptosis, apical mislocalization of the epidermal growth factor receptor, increased expression of β-catenin and c-myc, and inhibition of p21^{CIP1} (70).

The *cpk* mouse provides additional evidence that functional disruption of the primary apical cilia plays a role in PKD pathogenesis. The *cpk* mutation disrupts a novel gene and its protein product, cystin. In renal collecting duct epithelia, both epitope-tagged and endogenous cystin localize to the axoneme of primary apical cilia (56). Cystin has two putative myristoylation sites that are predicted to anchor the 145-amino acid protein to the inner leaflet of the ciliary axonemal membrane. While the *cpk* mutation is predicted to result in a null allele, *cpk* mutants have structurally normal cilia and no evidence for left-right patterning defects (125; Guay-Woodford LM, unpublished observations). These data are consistent with the hypothesis proposed by Brown and Murcia (12) that PKD-related proteins play distinct and perhaps independent roles in the primary cilia of the ventral node and ductal epithelia.

Polycystins Localize to the Primary Apical Cilia

Recent studies have demonstrated that polycystin-1 and polycystin-2 colocalize to the primary cilia of renal epithelial cells (114, 176) and may play integral roles in transducing mechanical signals caused by tubular flow (93). In cultured MDCK cells, bending of the primary apical cilia by either flow or mechanical force stimulates a rise in intracellular Ca^{2+} concentration (117). In the ciliary membrane, polycystin-1 (PC-1) appears to play a key role in sensing mechanical force and transduces this signal into a chemical response through direct interaction with polycystin-2 (PC-2), a Ca^{2+}-permeable cation channel (93). The Ca^{2+} influx into the primary cilium is sufficient to trigger Ca^{2+} release from intracellular stores via ryanodine receptors (93) and perhaps PC-2 (66). The increased Ca^{2+} concentration in intracellular microenvironments may then modulate specific transcription programs that regulate cellular proliferation, apoptosis, and differentiation. In this model, loss or dysfunction of PC-1 or PC-2, or cilia dysfunction in general, would impair the mechanosensing capacity of epithelial cells, causing defects in cellular differentiation and tubular integrity that in turn lead to cyst formation.

MURINE MODELS AND POTENTIAL TARGETS FOR PKD TREATMENT

Investigations in different murine PKD models have identified numerous abnormalities in the tubular epithelia, the interstitial compartment, and the extracellular matrix of cystic kidneys. These changes include *1*) dysregulation of epithelial cell proliferation and apoptosis (16, 53, 110, 122); *2*) aberrant growth factor expression (5, 32, 55, 89, 102); *3*) apical mislocation of a functional EGF receptor (109); *4*) abnormal transepithelial transport (43, 103, 108, 175); *5*) abnormal expression of epithelial cell adhesion molecules (128, 161, 168); *6*) increased expression of basement membrane constituents, e.g., laminins collagens, and fibronectin (14, 26, 27, 105, 133, 148); *7*) overexpression of extracellular matrix remodeling enzymes, the matrix metalloproteinases (MMPs), and their specific tissue inhibitors, TIMPs (123); *8*) increased production of vasoactive factors, chemokines, and proinflammatory cytokines (44); and *9*) alterations in steroid and bioactive lipid metabolism (6, 23).

Although diverse and not necessarily reproducible from one model to another, these abnormalities have provided the framework for evaluating interventions that target specific processes and pathways involved in PKD pathogenesis. These studies are briefly summarized in this section and Table 5. For a more comprehensive discussion, the reader is referred to an excellent review of treatment strategies in PKD (121).

Dietary Modulation

Dietary modulation in the *pcy* mouse and the Han:SPRD-*cy* rat strongly influences PKD development and progression. In these models of slowly evolving PKD, protein restriction attenuates disease progression, whereas a high-protein diet exacerbates renal cystogenesis (3, 101, 153). The mechanisms underlying these effects are not well defined, but high-protein intake has been shown to raise intracellular pH and inorganic phosphate levels, increase oxygen consumption and generate oxygen-free radicals, and enhance ammoniogenesis (reviewed in Ref. 121). Oxidative stress (78, 155), generation

Table 5. *Therapeutic interventions in murine PKD models*

Therapeutic Intervention	Mouse Models						Rat Models	
	cpk	*bpk*	*Tg737^{orpk}*	*pcy*	*Pkd2$^{WS25/-}$*	*Pkd1^{-}*	Han:SPRD	*pck*
Protein restriction				Yes			Yes	
Soy-based protein				Yes			Yes	
Flax seed							Yes	
Bicarbonate/citrate				No	No		Yes	No
ACEI							Yes	
ARB							Yes	
EGFR TK inhibitor		Yes					Yes	No
Taxanes	Yes		No	No			No	
Methylprednisolone				Yes			Yes	
MP inhibitor		Yes					Yes	
c-Myc antisense	Yes							
Pioglitazone						Yes		
Lovastatin							Yes	
V_2R antagonist	Yes							

Yes, ameliorating effect; no, no/deleterious effect; a space indicates effect has not been tested; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; EGFR TK inhibitor, epidermal growth factor receptor tyrosine kinase inhibitor; MP inhibitor, metalloproteinase inhibitor; V_2R, vasopressin receptor-2.

and release of ATP with its paracrine effect (137), and increased ammoniogenesis (157) have all been proposed as mechanisms that potentially contribute to PKD progression. Furthermore, dietary protein intake can influence renal cystic disease progression by modulating the activity of the intrarenal renin-angiotensin system and the expression of transforming growth factor-β (TGF-β) (101, 153).

In addition to dietary protein load, specific components within protein diets appear to modulate PKD progression. For example, soy protein-based diets attenuate the disease course in the Han:SPRD-*cy* rat and in the *pcy* mouse compared with PKD progression in animals fed standard casein-based diets (2, 99, 154). This beneficial effect has been attributed to phytoestrogens and soy-derived isoflavones, e.g., genistein, daidzein, and glycitein. However, it must be noted that genistein alone had no effect on PKD progression in Han:SPRD-*cy* rats (154). Dietary supplementation with flaxseed, a rich source of n-3 fatty acid and phytoestrogens, has also been reported to ameliorate the interstitial nephritis associated with PKD in Han:SPRD-*cy* rats (100).

Base Supplementation

In the Han:SPRD-*cy* rat, administration of sodium or potassium bicarbonate or sodium/potassium citrate markedly attenuates the development of PKD (147, 156). However, this beneficial effect has not been observed in other murine PKD models. In fact, the administration of sodium bicarbonate or sodium/potassium citrate to *pcy* mice has no beneficial effect and can be detrimental (156). Similarly, sodium bicarbonate feeding markedly accelerated PKD progression in *pck* rats (Torres VE, personal communication). Torres et al. (156) have postulated that these diametrically opposed treatment outcomes reflect the different nephron segments that undergo cystic change in each model. In the Han:SPRD-*cy* rat, cyst development occurs primarily in the proximal tubules, whereas in the *pcy* mouse and the *pck* rat, cysts originate in the distal tubules and collecting ducts. Different transport mechanisms drive acid-base transport in these nephron segments, suggesting that segment-specific metabolic pathways may modulate the development of renal cysts.

Renin-Angiotensin System Blockade

Vasoactive factors, e.g., angiotensin, endothelin, and nitric oxide, contribute to the proliferation of cystic epithelia, the progression of interstitial inflammation and fibrosis, and the decline in renal function in various PKD models (reviewed in Ref. 44). Several studies have demonstrated that the intrarenal renin-angiotensin system is activated in Han:SPRD-*cy* rats and targeted therapy attenuates disease progression (62–64). The administration of enalaprilat, an angiotensin-converting enzyme inhibitor, or losartan, an angiotensin II type 1 receptor antagonist to 3- to 4-wk-old Han:SPRD-*cy* rats significantly reduced renal cystic disease and the rate of decline in renal function, compared with other antihypertension agents. When administered to Han:SPRD-*cy* rats between 3 and 40 wk of age, enalaprilat and hydralazine exerted similar protective effects on renal function, but only enalaprilat reduced proteinuria and the progression of renal cystic disease, as assessed by kidney size (63).

ErbB Receptors and Tyrosine Kinase Inhibitors

Numerous studies have demonstrated that the EGF-transforming growth factor (TGF)-α-EGF receptor (EGFR) axis plays a pivotal role in renal cystogenesis and PKD progression. EGF and TGF-α are members of a large family of peptide ligands that bind to four, structurally related tyrosine kinase receptors known as ErbB receptors (42). Ligand binding triggers receptor dimerization, tyrosine kinase activation, and autophosphorylation, with the consequent stimulation of specific signaling cascades and targeted activation of transcription factors that modulate cell proliferation and cell differentiation.

While EGF expression at both the transcript and protein level is markedly downregulated in *cpk*, *pcy*, and Han:SPRD-*cy* kidneys (32, 69), the renal cyst fluid in these PKD models contains EGF-like peptides in mitogenic concentrations (69). In addition, physiologically active EGFR is mislocalized to the apical surface of cystic epithelial cells in *cpk*, *bpk*, and *orpk* kidneys (142). The apical EGFR (ErbB-1 receptor) binds EGF and TGF-α with high affinity and transmits a mitogenic signal when stimulated. Transgenic mice that overexpress TGF-α develop renal cystic disease, and renal expression of a TGF-α transgene accelerates PKD progression in *pcy* mice (36, 72). However, the impact of the mislocalized EGF-TGF-α-EGFR axis appears to be developmentally regulated, as EGF treatment in neonatal mice actually attenuates PKD progression (37, 91).

In an elegant proof-of-principle experiment, *+/orpk* mice were crossed with mice heterozygous for *waved-2* (*wa-2*), a hypomorphic allele that attenuates EGFR tyrosine kinase activity (124). Mutants homozygous for both *orpk* and *wa-2* had a significant reduction in collecting duct cysts and improved renal function compared with age-matched *orpk*/*orpk* littermates.

In the *bpk* model, treatment with tyrosine kinase inhibitors, such as tyrphostin or genistein, induced proximal tubule cyst regression in metanephric organ cultures (120) and attenuated collecting duct cyst formation in postnatal kidney explants (144). Furthermore, whole animal experiments demonstrated that administration of EKI-785, a specific EGFR tyrosine kinase inhibitor, markedly reduced collecting duct cyst formation, improved renal function, and prolonged survival in *bpk* mice (143).

Unfortunately, this therapeutic effect was not observed in the *pck* rat (Torres VE, personal communication). Therefore, while apical mislocalization of a functional EGF-TGFα-EGFR axis is a common feature of human and murine PKD epithelia, abnormalities in this pathway alone are not sufficient to explain renal cyst formation and PKD pathogenesis.

Taxanes

Woo et al. (170) first demonstrated, and other investigators have subsequently confirmed, that treatment of *cpk* mice with paclitaxel (taxol) causes significant attenuation in renal cystic disease progression and prolonged survival. Similar protective effects were observed with other taxanes, in direct proportion to their in vitro activity in binding and stabilizing microtubule assembly (169). In comparison, taxane treatment has no efficacy in *orpk*, *bpk*, and *pcy* mice or Han:SPRD-*cy* rats (77, 141), suggesting that the PKD-ameliorating mechanism is specific to the *cpk* model.

Anti-Inflammatory Agents and MMP Inhibitors

In addition to epithelial proliferation, PKD progression is characterized by interstitial inflammation and fibrosis. Inflammation develops early with intrarenal expression of chemokines, cytokines, and other inflammatory mediators (44). Methylprednisolone, a steroidal anti-inflammatory agent, has been shown to attenuate the slowly progressive PKD expressed in *pcy* mice and Han:SPRD-*cy* rats (34). However, the effect of anti-inflammatory agents has not been examined in models with more rapidly evolving PKD.

Interstitial fibrosis and extracellular matrix abnormalities are also well-described in PKD. MMPs, a group of zinc-dependent enzymes that modulate matrix remodeling and turnover, have been implicated in the pathogenesis of PKD. Increased intrarenal expression of both MMPs and TIMPs have been demonstrated in kidneys of both *cpk* mice and Han:SPRD-*cy* rats (90, 123, 132).

In Han:SPRD-*cy* rats, treatment with batimastat, a broad-spectrum MMP inhibitor, reportedly decreased cyst number and kidney weight (98). In *bpk* mice, WTACE2, a competitive inhibitor of TNF-α-converting enzyme, attenuated renal cyst formation and preserved renal function (22). TNF-α-converting enzyme is a metalloproteinase that cleaves the membrane-bound precursors of TNF-α, a major inflammatory mediator, and TGF-α, an EGFR ligand to release the active, secreted proteins.

Modulation of c-myc Expression

Expression of the protooncogene c-myc is upregulated in several murine PKD models (18, 70, 158). However, targeted modulation of c-myc expression in two different models has yielded apparently conflicting results. In *cpk* mice, daily treatment from postnatal *days 7–20* with a c-myc antisense oligomer decreased kidney size, reduced the cystic change, and improved renal function (126). In contrast, recent studies in a *Pkd1*$^{-/-}$ model have demonstrated that c-myc expression is downregulated in embryonic kidneys (87). The thiazolidinediones, a class of peroxisome proliferator-activated receptor-γ agonists, upregulate the expression of c-myc and β-catenin. Maternal administration of the thiazolidinedione pioglitazone upregulated expression of c-myc and β-catenin in Pkd1$^{-/-}$ kidneys and inhibited cystogenesis. Whether this result involves modulation of β-catenin expression alone, effects on both β-catenin and c-myc expression, or some other mechanism involved in cell cycle regulation or differentiation remains to be defined.

Single-Model Observations

Two additional agents deserve mention. Lovastatin, an hydroxymethylglutaryl-CoA reductase inhibitor, has been shown to attenuate the development of renal cystic disease in Han:SPRD-*cy* rats, possibly by inhibiting farnesylation of the Ras proteins (41). OPC31260, a relatively specific vasopressin-2 receptor (AVPV2R) antagonist, reduced renal insufficiency and slowed renal cystic disease progression in *cpk* mice (39). While the PKD-modulating effect of each agent has been studied only in single models, both drugs appear to have minimal toxicity and their efficacy in treating PKD deserves further investigation.

CONCLUSIONS

Despite the extensive studies in murine models with numerous agents, there is no consensus regarding effective treatment strategies in PKD. While targeted inhibition of the EGF-TGF-α-EGFR axis has shown great promise in the *bpk* and *orpk* models, preliminary studies have yielded disappointing results in the *Pkd2*$^{WS25/-}$ mouse and the *pck* rat. These data are somewhat surprising given that apical mislocalization of a functional EGF-TGF-α-EGFR axis has been demonstrated in human PKD epithelia (25). However, perhaps a different conclusion should be drawn from this apparent paradox. That is, defects in the EGF-TGF-α-EGFR axis may be necessary, but not sufficient, for renal cyst formation in all models.

PKD pathogenesis more likely involves a complex set of cellular processes and cell-matrix interactions, including the pathways that signal through the EGF-TGF-α-EGFR axis, PKA, β-catenin, c-myc, and p21^{CIP}. In addition, recent data demonstrate that mechanotransduction pathways associated with the primary apical cilia may play critical roles in modulating cellular proliferation, differentiation, and apoptosis. As these cilia-associated pathways are elucidated, new therapeutic targets and strategies will be defined.

More than a decade ago, Grantham (45, 46) proposed that PKD therapy should be modeled on the multitarget protocols used to treat neoplasias. With the availability of numerous, well-characterized murine PKD models, the elucidation of their genetic defects, the rapid expansion of new pathogenic insights, and the development of innovative, target-specific pharmaceuticals, such multiagent studies are now feasible and should be pursued.

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