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Polycystic Liver Disease: Advances in Understanding and Treatment

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Abstract

Polycystic liver disease (PLD) is a group of genetic disorders characterized by progressive development of cholangiocyte-derived fluid-filled hepatic cysts. PLD is the most common manifestation of autosomal dominant and autosomal recessive polycystic kidney diseases and rarely occurs as autosomal dominant PLD. The mechanisms of PLD are a sequence of the primary (mutations in PLD-causative genes), secondary (initiation of cyst formation), and tertiary (progression of hepatic cystogenesis) interconnected molecular and cellular events in cholangiocytes. Nonsurgical, surgical, and limited pharmacological treatment options are currently available for clinical management of PLD. Substantial evidence suggests that pharmacological targeting of the signaling pathways and intracellular processes involved in the progression of hepatic cystogenesis is beneficial for PLD. Many of these targets have been evaluated in preclinical and clinical trials. In this review, we discuss the genetic, molecular, and cellular mechanisms of PLD and clinical and preclinical treatment strategies.

Keywords

polycystic liver disease; cholangiocytes; cystogenesis; genetics; mechanisms; therapy

INTRODUCTION

Polycystic liver disease (PLD) is a group of genetic disorders characterized by the progressive growth of cholangiocyte-derived fluid-filled hepatic cysts. PLD was first described in 1856 as a pathological condition associated with polycystic kidney disease (PKD), and the existence of PLD as an isolated disorder was suggested in 1925 (1). The genetic landscape of PLD consists of 12 disease-causative genes. Nevertheless, multiple cases of PLD are still genetically unresolved.

PLD is classified as mild, moderate, and severe (2). Most individuals with PLD are asymptomatic, but in a subpopulation of patients, hepatomegaly leads to impaired liver function and, rarely, to liver failure requiring liver transplantation. Existent therapies for

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DISCLOSURE STATEMENT

T.V.M. and N.F.L. are inventors on US Patent 8,232,241 B2 for treating liver diseases.

PLD patients include conservative management and nonsurgical and surgical options; off-label use of somatostatin analogs is the only currently available pharmacological treatment (3–6).

In this review, we discuss the clinical features of PLD, pathogenetic mechanisms of hepatic cystogenesis, and clinical and preclinical therapeutic options for PLD.

PLD

As of today, the PLD family includes (*a*) PLD associated with autosomal dominant PKD (ADPKD) (prevalence 1:400), (*b*) PLD associated with autosomal recessive PKD (ARPKD) (prevalence 1:20,000), (*c*) isolated autosomal dominant PLD (ADPLD) (prevalence 1:100,000), and (*d*) PLD with undetected mutations (3, 7–10). The focus of the current review is on PLD with a known genetic background.

The most common form of PLD is associated with ADPKD, a life-threatening hereditary (typically adult-onset) disorder characterized by cyst formation and enlargement in the kidney and other organs. The occurrence and disease severity correlate with age and are sex dependent (3, 9, 10). Up to 58% of patients develop hepatic cysts between the ages of 15 and 24 years old, up to 85% between 25 and 34 years old, and up to 94% between 35 and 46 years old. The majority of symptomatic PLD patients (up to 94%) are women (11).

ARPKD is a fibrocystic disease of the kidney and liver, commonly with a childhood onset. Clinically apparent hepatic involvement occurs in ~45 % of ARPKD cases and is characterized by bile duct dysplasia due to ductal plate malformation, congenital hepatic fibrosis, portal hypertension, and hepatosplenomegaly (12, 13).

In contrast to PKD-associated PLD, ADPLD is characterized by the presence of liver cysts with no or few kidney cysts. ADPLD manifests between 40 and 60 years of age. The number and volume of cysts in ADPLD are typically greater than in ADPKD-associated PLD (14).

PLD is diagnosed by the presence of at least 10 hepatic cysts (4, 15). However, patients with a family medical history can be diagnosed by the presence of 4 cysts (16). Hepatic cysts have different sizes and shapes and are filled with cystic fluid (Figure 1). Liver function in most PLD patients remains normal. Independent of liver cyst burden, ~20% of patients have elevated γ-glutamyl transferase, alkaline phosphatase, and total bilirubin, and ~45% of patients have increased levels of CA-19–9, which positively correlates with liver volume and/or cyst infection (11, 17).

Progressive cyst growth correlates with enlargement of the liver, which increases in volume by up to 3.7% annually. In some patients, the liver can grow to up to 10 times the normal size, containing from 1 to 10 L of fluid. Both liver cysts and parenchyma contribute to hepatomegaly (2). Enlarged livers cause abdominal pain, nausea, vomiting, and early satiety, followed by weight loss, anorexia, shortness of breath, discomfort, and sleep apnea, affecting quality of life (2, 18–20).

MECHANISMS OF HEPATIC CYSTOGENESIS

We consider the mechanisms of hepatic cystogenesis as a sequence of the primary (mutations in PLD-causative genes), secondary (initiation of cyst formation), and tertiary (progression of hepatic cystogenesis) interconnected molecular and cellular events in cholangiocytes (Figure 2).

PRIMARY MOLECULAR EVENTS: MUTATIONS IN PLD-CAUSATIVE GENES

Genetically, PLD is a monogenic disease, but allelically and phenotypically it is a heterogeneous disease (21). Mutations in six genes (i.e., *PKD1*, *PKD2*, *GANAB*, *LRP5*, *DNAJB11*, and *ALG9*) cause ADPKD-associated PLD. Mutations in two genes (i.e., *PKHD1* and *DZIP1L*) result in ARPKD-associated PLD. ADPLD is caused by mutations in seven genes (i.e., *PRKCSH*, *SEC63*, *LRP5*, *GANAB*, *ALG8*, *SEC61B*, and *PKHD1*) (Figure 2a) (5, 9, 22–24). The number of PLD-causative genes and the observations that mutations in the same gene may cause both PKD-associated PLD and ADPLD emphasize the complexity of PLD genetics. It has been proposed that the genetic spectrum of PLD expands beyond the known 12 PLD-causative genes, and that mutations in more than one gene or activation/inhibition of gene modifiers might determine the severity of PLD (24).

Autosomal Dominant Polycystic Kidney Disease-Associated PLD: Genes and Proteins

The genetic nature of ADPKD was first suggested in 1925 and was accepted by 1957 (12). The *PKD1* gene was identified in 1985; the second gene, *PKD2*, was reported in 1993 (25). To date, more than 1,650 mutations in *PKD1* and 250 mutations in *PKD2* cause approximately 80% and 15% of ADPKD cases, respectively, and 94% of ADPKD patients develop PLD (26).

PKD1 encodes the glycoprotein polycystin 1 (PC1) that functions as a G protein-coupled receptor (GPCR) (21, 27). The protein product of *PKD2*, membrane glycoprotein polycystin 2 (PC2), is a member of the transient receptor potential (TRP) family of ion channels (24). PC2 forms homotetramers and a heterotetramer with PC1 regulating $[Ca^{2+}]_i$ (21, 27).

Mutations in *GANAB*, *LRP5*, *DNAJB11*, and *ALG9* account for a small percentage of total ADPKD cases (24). As of today, 7% of ADPKD cases are still genetically unresolved.

GANAB encodes the catalytic α subunit of glucosidase II (GII), an endoplasmic reticulum (ER) protein responsible for *N*-linked glycosylation, a key quality-control process that regulates folding, maturation, and trafficking of membrane and secreted proteins. To date, several mutations of *GANAB* have been described (28–30).

The protein product of *LRP5*, a low-density lipoprotein receptor-related protein 5 (LRP5), is a part of the LRP5/LRP6/Frizzled coreceptor complex (10). LRP5, together with the Frizzled receptors, binds to the Wnt proteins, activating Wnt signaling (9). The LRP5 gene mutations are predicted to be loss-of-function mutations, although the exact role of LRP5 in hepatic cystogenesis remains unclear (3).

DNAJB11 encodes a soluble ER protein DNAJB11 (DNAJ/HSP40 homolog, subfamily B, member 11). DNAJB11 stabilizes the transfer of the translated peptides through the SEC61-SEC62-SEC63 channel to assure the correct protein trafficking and degradation. A dosage reduction of DNAJB11 is thought to cause cyst formation. To date, five different *DNAJB11* pathogenic variants have been described (31).

Newly implicated in ADPKD and ADPKD-associated PLD, the *ALG9* gene encodes ALG9, an ER protein involved in peptide glycosylation (32). The specific role of ALG9 in hepatic cystogenesis is unknown.

Mutations in *PKD1*, *PKD2*, and *GANAB* cause mild to severe PLD, while mutations in *DNAJB11*, *LRP5*, and *ALG9* result in mild to moderate PLD (33). The severity of PLD does not directly correlate with the type of mutation (34).

Autosomal Recessive Polycystic Kidney Disease-Associated PLD: Genes and Proteins

ARPKD-associated PLD is caused by mutations in two genes, *PKHD1* and *DZIP1L*, and is characterized by dysgenesis of the hepatic portal triad resulting from defective remodeling of the ductal plate, hyperplastic biliary ducts, and congenital hepatic fibrosis. In individuals surviving the neonatal period, portal hypertension and cholangitis are the major complications (24, 33, 35, 36).

PKHD1 encodes fibrocystin (FC), a transmembrane protein that functions as a membrane-bound receptor involved in regulation of proliferation and morphogenesis (37).

DZIP1L encodes DAZ interacting protein 1 like (DZIP1L), a soluble zinc-finger protein localized to the centrioles and at the distal end of the basal body (35). *Dzip1l* loss-of-function mice develop ductal plate malformations, a pathological characteristic of ARPKD-associated PLD (35).

Autosomal Dominant PLD: Genes and Proteins

Mutations in seven genes, *PRKCSH*, *SEC63*, *LRP5*, *GANAB*, *ALG8*, *SEC61B*, and *PKHD1*, have been implicated in ADPLD (8, 24, 28, 30, 38, 39). Despite such genetic heterogeneity, only 40% of cases are assigned to mutations in these genes; the rest of the cases are still unresolved. Mutations in *PRKCSH*, *SEC63*, and *GANAB* cause mild to severe PLD; mutations in *ALG8*, *SEC61B*, and *LRP5* result in mild to moderate PLD; and mutations in *PKHD1* result in congenital hepatic fibrosis and small liver cysts (33).

The protein product of *PRKCSH*, hepatocystin, is a noncatalytic β subunit of GII localized to the ER (40). Hepatocystin is involved in processing and quality control of newly synthesized glycoproteins (41). Mutations in *PRKCSH* result in abnormal hepatocystin, suggesting that ADPLD arises from a loss of function of this protein (10, 40).

SEC63 encodes an integral membrane protein of the ER, SEC63, which is a part of the multicomponent complex responsible for translocation of the integral membrane and secreted proteins. Mutations in *PRKCSH* and *SEC63* together account for less than one-third of ADPLD cases (42, 43).

Mutations in the *ALG8* and *SEC61B* genes have also been linked to ADPLD (10). *ALG8* encodes alpha-1,3-glucosyltransferase (ALG8), an ER integral membrane protein. The *SEC61B*-encoded product is a component of the SEC63 protein complex in the ER. Both ALG8 and SEC61 control protein translocation and membrane insertion. Together, they account for ~4% of ADPLD cases (30).

Mutations in the *LRP5* and *PKHD1* genes (described above) may cause ADPLD and, respectively, ADPKD- and ARPKD-associated PLD. The detection rate of *LRP5* and *PKHD1* pathogenic variants in ADPLD is less than 1 % (9).

SECONDARY MOLECULAR AND CELLULAR EVENTS: INITIATION OF HEPATIC CYSTOGENESIS

Autosomal Dominant Polycystic Kidney Disease-Associated PLD

A heterozygous germline mutation in the *PKD1* or *PKD2* genes itself does not initiate hepatic cystogenesis. To initiate cyst formation, cholangiocytes must lose the wild-type allele after a second somatic mutation or a second-hit mutation at other loci. A cholangiocyte with a somatic mutation is then transformed into a hepatic cyst stem cell [i.e., a single PLD cholangiocyte (PLDC)] with aberrant expression and function of PC1 or PC2 and defective PC1- or PC2-mediated signaling (9). Clonal expansion of a PLDC initiates the formation of elementary hepatic cysts (9).

Thus, the transformation of healthy cholangiocytes into PLDCs with aberrant PC1 or PC2 expression and functions and the clonal expansion of PLDCs are the earliest molecular and cellular events that initiate hepatic cystogenesis (Figure 2b).

Autosomal Recessive Polycystic Kidney Disease-Associated PLD

The biliary cyst formation in ARPKD-associated PLD is primarily triggered by missense and truncating mutations in the *PKHD1* gene and, in rare cases, by mutations in *DZIP1L* (21). The functions of proteins, FC, and DZIP1L encoded by these two genes remain obscure (24).

The initiation of hepatic cytogenesis in ARPKD-associated PLD is presumably linked to the embryological arrest of ductal plate development, which leads to the inability of biliary precursor cells to differentiate, defective maturation of primitive bile ducts, and/or abnormal bile duct enlargement (23).

FC is localized to cilia in healthy cholangiocytes but not in PLDCs, affecting ciliary morphology and sensory and signaling functions (44). DZIP1L normally is localized to the centrioles and the ciliary basal bodies maintaining the periciliary diffusion barrier at the ciliary transition zone. Mutated *DZIP1L* causes defects in the diffusion barriers, preventing delivery of sensory/signaling proteins to cilia (35). Thus, ductal plate malformation and ciliary abnormalities are presumably the earliest phenotypic manifestations of mutated *PKHD1* and *DZIP1L* (Figure 2b).

Autosomal Dominant PLD

The protein products of ADPLD-causative genes, except for LRP5, reside in the ER and are involved in protein glycosylation, folding, quality control, and translocation. Correctly assembled proteins are transported out of the ER to their cellular location. Mutations in the *PRKCSH*, *SEC63*, *ALG8*, *GANAB*, and *SEC61B* genes compromise biogenesis and trafficking of many proteins, including PC1 (Figure 2b) (30). Mutations in *GANAB* may cause ADPKD-associated PLD and ADPLD, suggesting that hepatic cystogenesis in both diseases is likely driven by defects in PC1 maturation (22, 23). In contrast to *ALG8*, *GANAB*, and *SEC61B*, the pathogenic variants in *PKHD1* contribute to ADPLD without affecting PC1 biogenesis, presumably via the aberrant PC1-FC interaction (22).

Missense variants in *LRP5* coexist with *PKHD1* variants, suggesting that interaction of these two genes may cause cyst growth in patients with mutated *PKHD1* (22).

Thus, hepatic cystogenesis in ADPLD is initiated by the aberrant expression and functions of the ER proteins PRKCSH, SEC63, ALG8, SEC61B, and GANAB, which in many cases reduce the steady-state levels of PC1. The interaction of the protein products of the ADPLD-causative genes with PC1 supports the hypothesis that PC1 is a master regulator of the intersecting pathways in the initiation of hepatic cystogenesis (22, 23).

TERTIARY MOLECULAR AND CELLULAR EVENTS: PROGRESSION OF HEPATIC CYSTOGENESIS

The abnormalities in signaling functions of cholangiocyte primary cilia and altered cilia-dependent intracellular mechanisms, including enhanced proliferation and fluid secretion, are crucial for the progression of hepatic cystogenesis in ADPKD-associated PLD and ADPLD (Figure 2c).

ADPKD- and ARPKD-associated PLD belong to cholangiociliopathies, a group of liver diseases linked to the morphological and functional defects in cholangiocyte cilia (7, 45). In healthy cholangiocytes, PC1, PC2, and FC are localized to the primary cilium, a sensory organelle that extends from the apical plasma membrane into the bile duct lumen and detects, amplifies, and integrates diverse extracellular stimuli into the intracellular signaling and functional responses (46–48). According to a plausible hypothesis, in healthy cells, extracellular stimuli (e.g., fluid flow) activate the PC1-PC2 complexes in cilia, triggering a cilia-mediated $[Ca^{2+}]_i$ response (48, 49). However, this hypothesis is now under revision because recent studies demonstrated that the PC1-PC2 complexes can induce PC2-dependent changes in the concentration of ciliary Ca^{2+} without affecting cytoplasmic Ca^{2+} (50).

In contrast to cilia in healthy cholangiocytes, malformed PLDC cilia do not express PC1, PC2, or FC, resulting in altered ciliary sensory and signaling functions and interrupted $[Ca^{2+}]_i$-cyclic adenosine monophosphate (cAMP) cross talk (44, 47, 48, 51). Aberrant expression and ciliary localization of PC1 decrease the levels of $[Ca^{2+}]_i$, subsequently activating $[Ca^{2+}]_i$-dependent cAMP signaling (52). Another potential mechanism of the cAMP increase in PLDC is overexpression and mislocalization of a cAMP-linked bile

acid receptor, TGR5 (Takeda G protein–coupled receptor 5) (53). Activation of the ciliary-localized TGR5 by bile acids inhibits cAMP in healthy cholangiocytes (54). In contrast, in PLDC, TGR5 is overexpressed, localized predominantly at the apical plasma membrane, and, when activated, accelerates PLD progression (53, 54). In PLD, bile acids (i.e., TGR5 ligands) accumulate in the cystic fluid and can act as extracellular stimuli, regulating cAMP-dependent hepatic cyst growth (23, 54, 55).

In ARPKD-associated PLD, mutated FC and DZIP1L drive functional abnormalities in cilia and the downstream signaling pathways, accelerating cholangiocyte proliferation and hepatic cystogenesis (22, 23).

In ADPLD, a disrupted interaction of the protein products of ADPLD-causative genes with PC1 affects cholangiocyte sensory and signaling functions and ciliary-mediated progression of hepatic cystogenesis (23).

The primary, secondary, and tertiary molecular and cellular events that underlie hepatic cystogenesis are interconnected, but the mechanisms of their interconnection are largely unknown. We found that more than 30 biological pathways, including intracellular signaling, cell cycle regulation, proliferation, and secretion, are altered in PLDC (Figure 3) (56–58). Importantly, many of these key processes of hepatic cystogenesis can be pharmacologically targeted, creating new possibilities for therapeutic opportunities in PLD.

THERAPEUTIC INTERVENTION

The treatment options for PLD depend on the severity of disease. Individuals without symptoms undergo conservative management (i.e., watchful waiting). Treatment of symptomatic patients includes nonsurgical and surgical options. Classification systems by Gigot and Schnelldorfer are commonly used to characterize the severity of PLD and to outline a potential treatment (Figure 4). In Gigot's classification scheme, there are three types of PLD. Type I is defined by the presence of fewer than 10 hepatic cysts that are more than 10 cm in diameter; type II is defined by multiple cysts with large areas of noncystic parenchyma; and type III is defined by small- and medium-sized cysts with only a few areas of unaffected parenchyma (59). Schnelldorfer's classification distinguishes four types of PLD. Type A is characterized by no or mild symptoms and cysts of any size. In type B, symptoms are moderate to severe; large and small cysts are present with multiple areas of noncystic parenchyma. Type C is characterized by severe symptoms; large and small cysts are present with reduced areas of noncystic parenchyma. Individuals with type D have severe symptoms; large and small cysts are present with significantly reduced areas of noncystic parenchyma (59, 60). Individuals with mild symptoms may experience back or flank pain. Moderate symptoms affect quality of life and include early satiety; nausea; bloating; gastroesophageal reflux; dyspnea; and abdomen, flank, or back pain. Individuals with severe PLD may experience liver displacement, stomach compression cause, early satiety, weight loss, and sarcopenia (61).

In patients with Gigot type I PLD, cyst aspiration and sclerosis are the recommended treatment. The success of the procedure correlates with the cyst size. Laparoscopic

fenestration of hepatic cysts (a less common procedure since the results are often short lived) is used in patients with multiple cysts in Gigot types I and II or Schnelldorfer type B PLD (62, 63). In individuals with Gigot type II or Schnelldorfer type C, the treatment includes combined hepatic resection and fenestration. A liver transplantation is reserved for patients with impaired liver function or for whom a liver resection is not feasible (Gigot type III or Schnelldorfer type D) (60). PLD patients are frequently treated with multiple therapeutic options and are often treated more than once during the disease course (15). As of today, off-label use of somatostatin analogs is the only pharmacological option in symptomatic patients for whom surgical intervention is technically challenging or not justified (24, 64, 65).

Progress in the understanding of PLD pathogenic mechanisms has led to the identification of multiple molecular targets that have been explored in clinical and preclinical trials (Figure 5).

CLINICALLY TESTED PHARMACOTHERAPIES

Somatostatin Analogs

Five Gαi protein–coupled somatostatin (SST) receptors (SSTR1 to SSTR5) are expressed in cholangiocytes (66, 67). Activation of the SST receptors in healthy cholangiocytes decreases cAMP, fluid secretion, and cell proliferation, the major cellular processes implicated in hepatic cystogenesis. Due to a short half-life of SST (~1–3 min), SST analogs with prolonged half-life [i.e., octreotide (~2 h), lanreotide (~2 h), and pasireotide (~12 h)] have been developed. Octreotide and lanreotide have a high affinity to SSTR2 and SSTR3 and a moderate affinity to SSTR5. Pasireotide binds with a high affinity to SSTR1, SSTR2, SSTR3, and SSTR5 (66, 67).

Our group was the first to demonstrate the promising role of SST analogs in PLD. We found that octreotide inhibits growth of hepatic cysts in PCK rats by decreasing cholangiocyte proliferation and cAMP levels (66). Comparative studies in PCK rats also demonstrated that pasireotide suppressed hepatic cystogenesis more effectively than octreotide (67).

A number of clinical trials evaluated the therapeutic effects of octreotide and lanreotide in PLD (19, 20, 68, 69). Collectively, these trials established that (*a*) the liver volume is decreased by 1.4% to 4.95% after 6–12 months of treatment; (*b*) the reduction in liver volume is maintained for 24 months posttherapy; (*c*) little or no further reduction in liver volume is noted upon continued treatment; (*d*) when the treatment is stopped, the liver volume begins to increase; (*e*) SST analogs are more effective in patients with the most severe PLD; (*f*) some patients do not respond to the treatment; (*g*) adverse events, such as abdominal pain and diarrhea, are well tolerated and quickly resolved; and (*h*) the quality of life is improved. Incidences of cholelithiasis, cholecystitis, and hepatic cyst infections have been reported in fewer than 5% of lanreotide-treated individuals (18, 19, 65, 70–72). As of today, off-label use of octreotide and lanreotide is the only available pharmacotherapy for individuals with PLD.

The effects of pasireotide have also been evaluated in patients with severe PLD in a randomized trial. Pasireotide reduced liver volume by ~3% but did not improve the quality of life, likely due to the high rates of diabetes and hyperglycemia (73). Another small trial showed that pasireotide administered 2 weeks before and 2 weeks after aspiration sclerotherapy did not affect cyst reduction (74).

Mammalian Target of Rapamycin Inhibitors

Mammalian target of rapamycin (mTOR) regulates multiple cellular processes including cell proliferation, metabolism, protein synthesis, and autophagy. In PLDC, mTOR is overexpressed (75). An mTOR inhibitor, rapamycin, attenuated hepatic cyst grown in *Pkd2KO* mice, an animal model of PLD (76). In PCK rats, sirolimus (formerly rapamycin) failed to reduce hepatic cystogenesis, whereas another mTOR inhibitor, everolimus, prevented cyst enlargement (77, 78).

Sirolimus and everolimus were also examined in clinical trials. In an individual with ADPKD-associated PLD, sirolimus decreased liver volume by ~12% (79). Comparative studies in PLD patients that assessed the reduction of the liver volume in response to octreotide alone or in combination with everolimus showed no additive effects of everolimus (80). Thus, the role of mTOR inhibitors in PLD treatment remains unclear.

Ursodeoxycholic Acid

Ursodeoxycholic acid (UDCA), an endogenous bile acid with choleretic and hepatoprotective properties, halted cyst growth in patients with enlarged polycystic livers (81). In a randomized clinical trial in individuals with severe ADPKD-associated PLD, UDCA delayed the growth of hepatic cysts after 24 weeks of treatment (82).

THERAPEUTIC TARGETS TESTED IN ANIMAL MODELS OF PLD

Autophagy

Autophagy is altered in PLDC, contributing to hepatic cyst growth. Molecular and pharmacologic intervention in autophagy reduced the proliferation of PLDC cholangiocytes in vitro and the growth of hepatic cysts in three-dimensional cultures. Hydroxychloroquine, an autophagy inhibitor, efficiently decreased hepatic cystogenesis in PCK rats (56).

TGR5

TGR5 is a cAMP-linked GPCR activated by bile acids. Our group was the first to report overexpression of TGR5 in PLDC and an elevated concentration of TGR5 ligands in the cystic fluid (54, 55). Activation of TGR5 in PLDC further increased cAMP and proliferation. In PCK rats, a TGR5 agonist, oleanolic acid, worsened hepatic cystogenesis. In contrast, genetic elimination of *Tgr5* reduced hepatic cystogenesis in $Tgr5^{-/-}$:$Pkhd1^{del2/del2}$ mice (54). These data suggest to us that TGR5 inhibition is a promising approach in PLD treatment. Indeed, we showed that novel TGR5 antagonists developed by us effectively decreased cAMP levels, cholangiocyte proliferation, and cyst growth in in vitro and in vivo models of PLD (54).

Transient Receptor Potential Vanilloid 4

TRP vanilloid 4 (TRPV4), a calcium channel, is expressed in cilia of healthy cholangiocytes and functions as a chemosensor (83, 84). In PLDC, TRPV4 is overexpressed and mislocalized, being present intracellularly rather than in cilia. A specific TRPV4 activator, GSK1016790A, restored $[Ca^{2+}]_i$ in PLDC, decreasing proliferation and cyst growth in vitro. However, only marginally reduced hepatic cystogenesis was observed in GSK1016790A-treated PCK rats (84).

Histone Deacetylase 6

Histone deacetylase 6 (HDAC6) is overexpressed in human and rodent PLDC. Several HDAC6 inhibitors (i.e., tubastatin A, tubacin, ACY1215, ACY738, and ACY241) and a pan-HDAC inhibitor, panobinostat, decreased hepatic cystogenesis in PCK rats by reducing cholangiocyte proliferation (85, 86).

Cell Cycle Protein CDC25A

Cell cycle–related proteins, including the master cell cycle regulator CDC25A, are overexpressed in PLDC (57). Genetic reduction of *Cdc25a* decreased cell proliferation and hepatic cystogenesis in $Cdc25a^{-/-}$:$Pkhd1^{del2/del2}$ mice (5, 51, 87). Two CDC25A inhibitors, menadione and PM-20, also suppressed hepatic cystogenesis in PCK rats by reducing Cdc25A activity (87).

Extracellular Matrix Remodeling and Matrix Metalloproteinases

Extracellular matrix (ECM) remodeling mediated by matrix metalloproteinases (MMPs) is essential for cyst expansion. Expression of MMP-3 is increased in PLDC. In PKC rats, the MMP-3 inhibitor marimastat decreased hepatic cystogenesis by reducing MMP hyperactivity (88). However, in clinical trials, marimastat showed musculoskeletal toxicity and thus does not appear to be a feasible therapy for PLD.

Endoplasmic Reticulum Stress

PLDCs are characterized by altered proteostasis (i.e., synthesis, folding, trafficking, and degradation of proteins), a markedly enlarged ER lumen, and hyperactivation of the proteasome. 4-phenyl butyric acid (4-PBA), an ER stress inhibitor, decreased hepatic cystogenesis in PCK rats by normalizing protein synthesis, folding, trafficking, and degradation and by reducing proteasome hyperactivity (89).

Posttranslational Protein Modification

Posttranslational modifications (including SUMOylation) are critical for proper protein functions. SUMOylation requires an enzymatic cascade consisting of heterodimer E1 activating enzyme (SAE1/UBA2), E2 conjugating enzyme (UBC9), and E3 ligase. In PCK rats, enhanced hepatic cystogenesis was associated with increased protein SUMOylation due to overexpression of SAE1, UBA2, and USB9. A UBC9-dependent SUMOylation inhibitor, S-adenosylmethionine, reduced proteosome activity, induced stress-related apoptosis, and attenuated cyst growth (90).

Adenylyl Cyclases

There are nine membrane-bound adenylyl cyclase (AC) isoforms and one cytosolic AC isoform. Cholangiocytes express at least seven ACs. One of the ACs, calcium-inhibitable AC5, has been implicated in PLD progression (91). The growth of biliary organoids formed by *PC2*-deficient cholangiocytes was reduced by two AC5 inhibitors, SQ22536 and NKY80. SQ22536 also suppressed cholangiocyte proliferation and attenuated hepatic cystogenesis in *PC2*-defective mice (92).

AMP-Activated Protein Kinase

The phosphorylation of AMP-activated protein kinase (AMPK), an upstream regulator of mTOR and CFTR, is reduced in PCK rats (93). Metformin, a biguanide drug, attenuated hepatic cystogenesis by increasing phosphorylation of AMPK, which subsequently suppressed phosphorylation of mTOR and ERK and expression of CFTR and AQP1 (93).

Vascular Endothelial Growth Factor Receptor 2

In $Pkd2^{WS25/-}$ and *Pkd2KO* mice, SU5416, an inhibitor of vascular endothelial growth factor receptor 2 (VEGFR2) and VEGFR1, decreased cholangiocyte proliferation and hepatic cystogenesis but did not affect these processes in *Pkd1KO* mice; this result suggests that underlying genetic background might determine a treatment outcome (94, 95).

Heat Shock Protein 90

Heat shock protein 90 (HSP90), a molecular chaperone, is required for stability of proteins involved in cell proliferation. In cholangiocytes of $Pkd1^{-/-}$ mice, inhibition of overexpressed HSP90 by a small molecule inhibitor, STA-2842, reduced the levels of two HSP90 client proteins, EGFR and ERK1/2, and inhibited hepatic cystogenesis (96).

Peroxisome Proliferator-Activated Receptors

Peroxisome proliferator-activated receptor gamma (PPAR-γ), a member of a family of nuclear hormone receptors, mediates inflammation, cell proliferation, and fibrosis. Two PPAR-γ agonists (a full agonist, pioglitazone, and a partial agonist, telmisartan) reduced hepatic cystogenesis in PCK rats, presumably by decreasing transforming growth factor β expression and ERK phosphorylation (97, 98).

The expression of PPAR-α, which promotes fatty acid β-oxidation and oxidative phosphorylation, is decreased in PLDC. In $Pkd1^{RC/RC}$ mice, fenofibrate, a PPAR-α agonist, reduced hepatic cystogenesis by increasing expression of PPAR-α (99).

COMBINATIONAL STUDIES

Considering that disturbances in multiple intracellular pathways underlie hepatic cystogenesis, a concurrent targeting of different pathways or synergistic targeting of different entities in a single pathway is an attractive concept. In PCK rats, a simultaneous administration of pasireotide and an autophagy inhibitor, hydroxychloroquine, attenuated hepatic cystogenesis more effectively than a single-drug treatment (56). Treatment of PCK

rats with an HDAC6 inhibitor, ACY-1215, and pasireotide also reduced hepatic cystogenesis to a higher degree than each drug alone (86).

Cotreatment of PCK rats with octreotide and pasireotide showed that the effects of this drug combination on liver cystogenesis were comparable with those of pasireotide-only treatment (100). An important finding of this study is that the drug combination reduced glucagon concentration, since hyperglycemia caused by pasireotide is an adverse clinical effect (73). ATGR5 antagonist, SBI-115, and pasireotide together decreased cAMP levels, PLDC proliferation, and cyst growth in vitro more efficiently than each drug alone, demonstrating an additive beneficial effect on PLD (54).

CONCLUSION

Despite genetic diversity, PLD is characterized by development and progressive growth of hepatic cysts. Clinical management of PLD depends on disease severity and includes watchful waiting, nonsurgical and surgical interventions, and limited drug options. Significant advances in our understanding of the genetics and pathogenic mechanisms of PLD have triggered identification of novel therapeutic targets, which have been tested and shown promise in vitro and in vivo, in both preclinical studies and clinical trials.

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LITERATURE CITED

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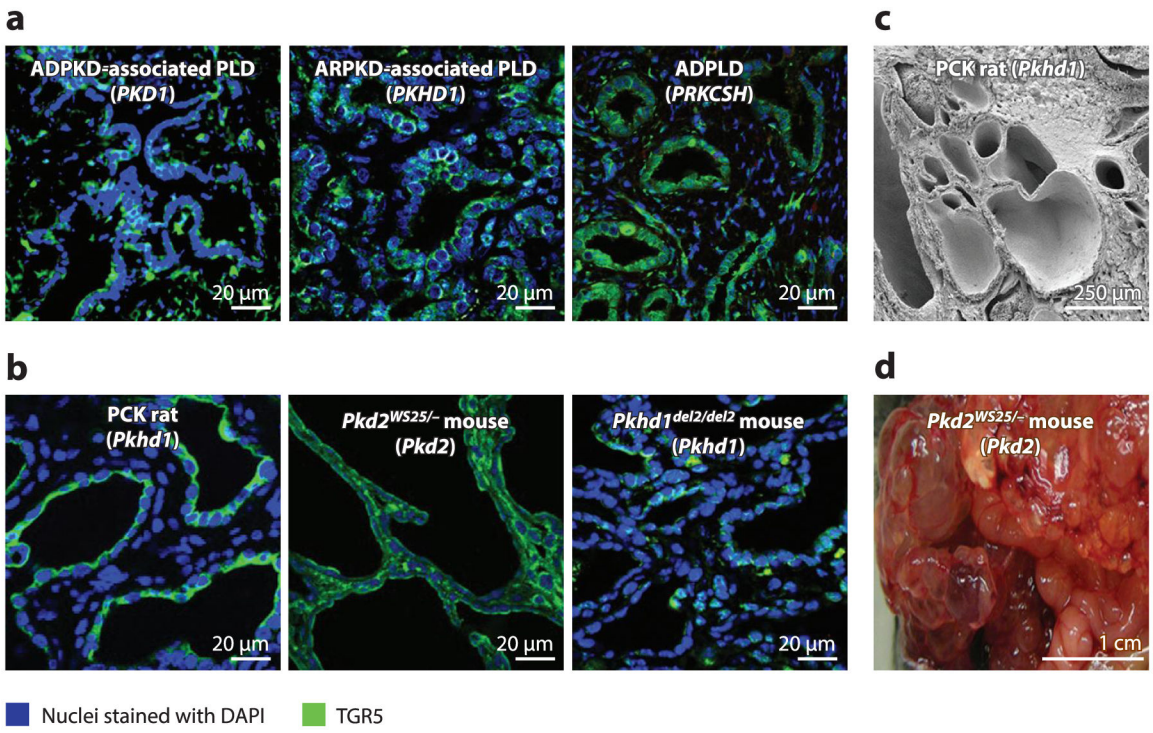


Figure 1.

Hepatic cystogenesis in (*a*) patients and (*b-d*) animal models with different forms of PLD. Disease-causative genes are shown in parentheses. Despite genetic heterogeneity, mutations in PLD-causative genes result in similar end points—multiple hepatic cysts of different sizes and shapes. (*a*,*b*) Immunofluorescence confocal microscopy. (*c*) Scanning electron microscopy. (*d*) Gross appearance. Abbreviations: ADPKD, autosomal dominant polycystic kidney disease; ADPLD, autosomal dominant polycystic liver disease; ARPKD, autosomal recessive polycystic kidney disease; PLD, polycystic liver disease; TGR5, Takeda G protein-coupled receptor 5. Panel *c* adapted from Reference 45 with permission from Elsevier.

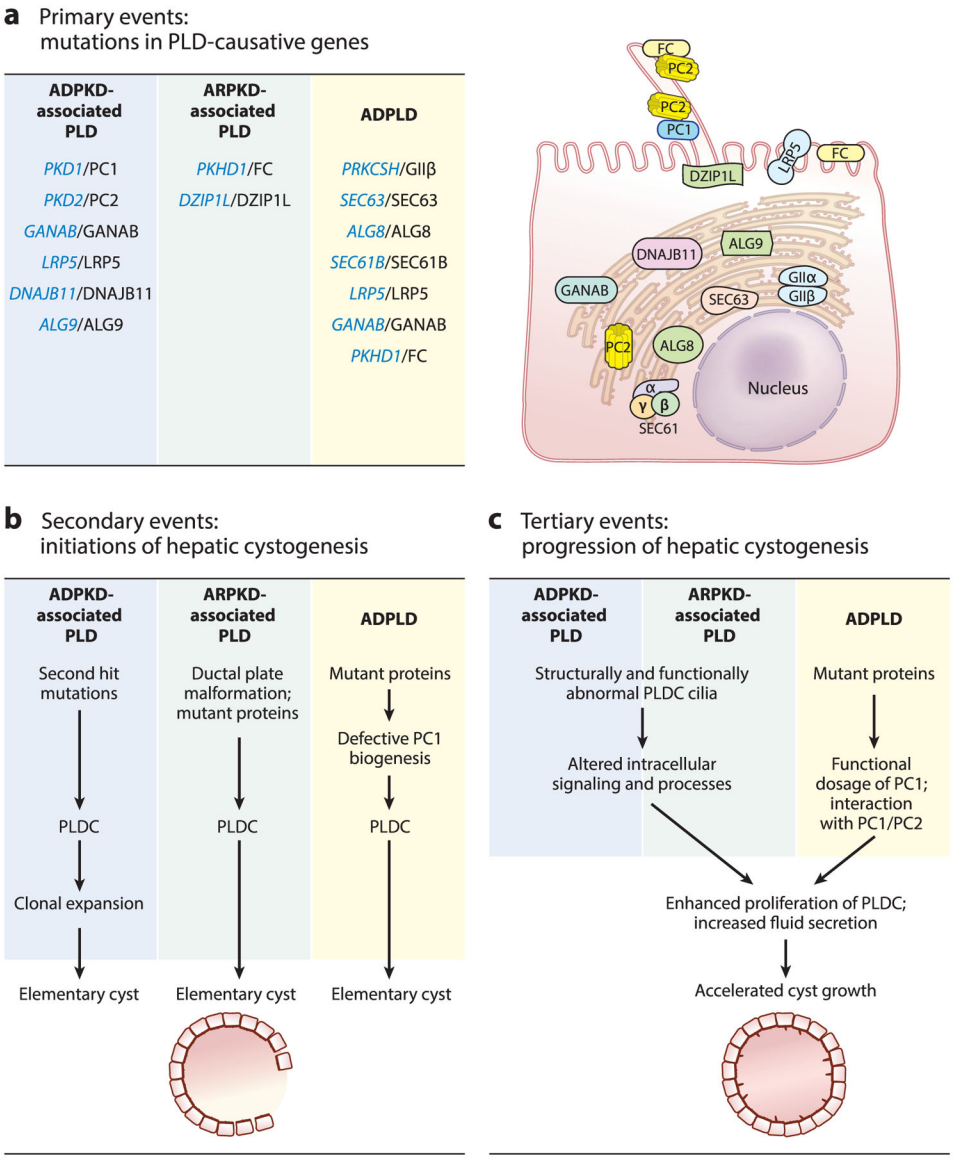


Figure 2.

The mechanisms of hepatic cystogenesis: a sequence of the interconnected molecular and cellular (*a*) primary, (*b*) secondary, and (*c*) tertiary events in cholangiocytes. In panel *a*, PLD-associated genes are shown in blue and respective protein products are shown in black. Abbreviations: ADPKD, autosomal dominant polycystic kidney disease; ADPLD, autosomal dominant polycystic liver disease; ARPKD, autosomal recessive polycystic kidney disease; PLD, polycystic liver disease; PLDC, polycystic liver disease cholangiocyte.

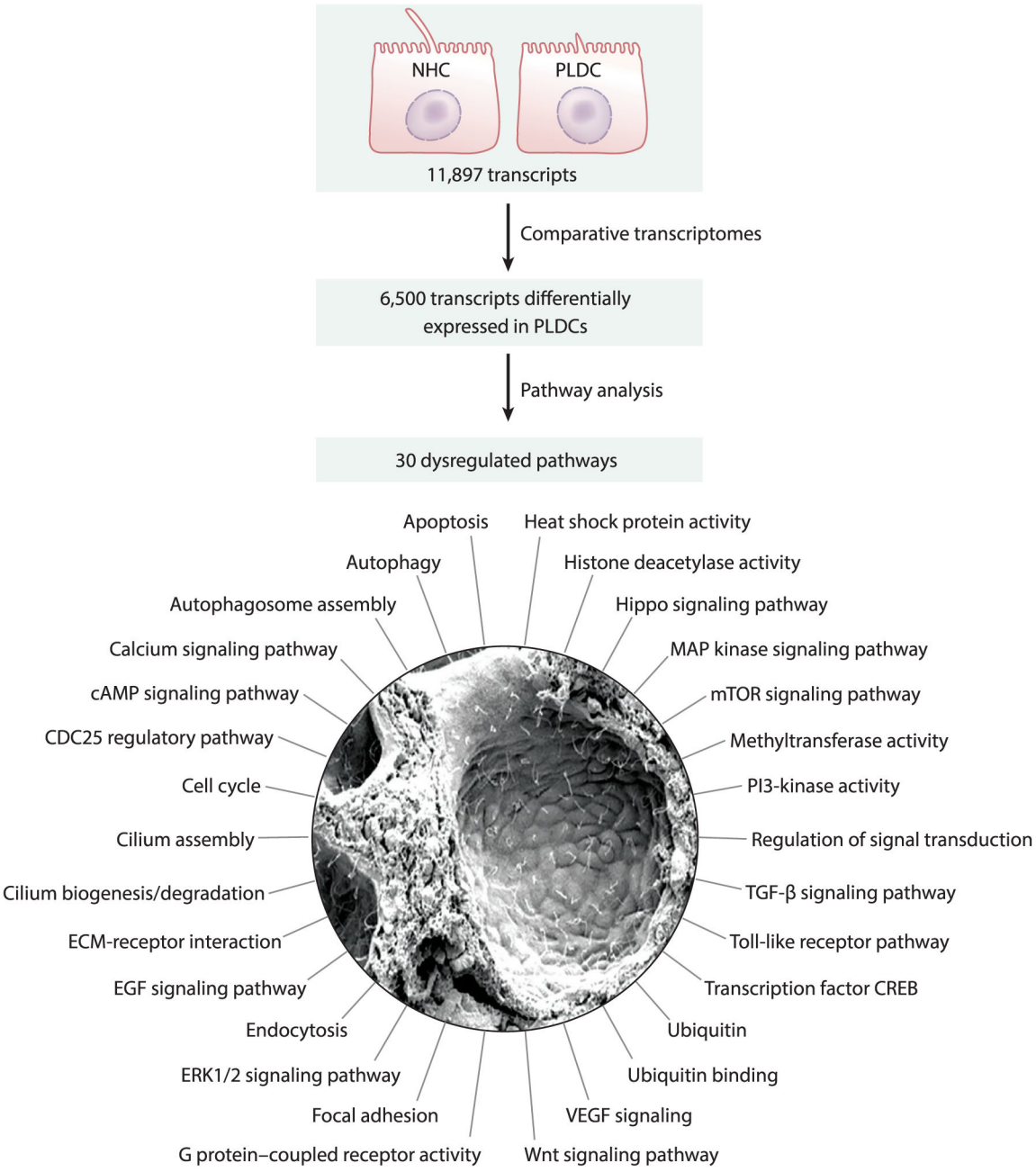


Figure 3.

Pathways dysregulated in PLD. Transcriptome profiling of NHCs and PLDCs revealed that out of 11,897 transcripts present in both cell lines, 6,500 transcripts were differentially expressed in PLDCs (i.e., up- or downregulated). Functional annotation clustering of these transcripts by the Kyoto Encyclopedia of Genes and Genomes pathways indicates 30 altered pathways in PLDCs. Abbreviations: cAMP, cyclic adenosine monophosphate; CDC25, cell division cycle 25; CREB, cAMP-response element-binding protein; ECM, extracellular matrix; EGF, endothelial growth factor; ERK, extracellular signal-regulated kinase; MAP, mitogen-activated protein; mTOR mammalian target of rapamycin; NHC, normal human

cholangiocyte; PI3, phosphoinositide 3; PLD, polycystic liver disease; PLDC, polycystic liver disease cholangiocyte; TGF, transforming growth factor; VEGF, vascular endothelial growth factor. Scanning electron microscope image adapted with permission from Reference 22.

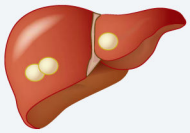
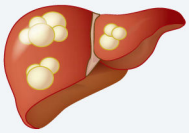
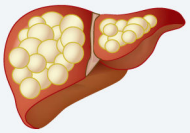
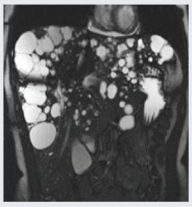
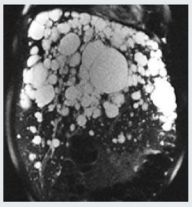
Gigot's classification criteria	**Type I**	**Type II**	**Type III**
Schnelldorfer's classification criteria	**Type A**	**Type B**	**Types C and D**
Graphical representation			
Magnetic resonance imaging			
Clinical presentation	<10 large isolated cysts	Multiple cysts; large areas of unaffected parenchyma	Multiple cysts; limited areas of unaffected parenchyma
Symptoms	None or mild	Moderate to severe	Severe
Treatment options	Cyst aspiration and sclerosis	Laparoscopic fenestration; hepatic resection	Liver transplantation
Pharmacotherapy	Somastostatin receptor analogs		

Figure 4.

Classification criteria for polycystic liver disease severity, clinical presentation, symptoms, and treatment options. Gigot and Schnelldorfer classifications are based on the number and size of the cysts and the remaining liver parenchyma. Abdominal magnetic resonance imaging images provided by Dr. M. Hogan.

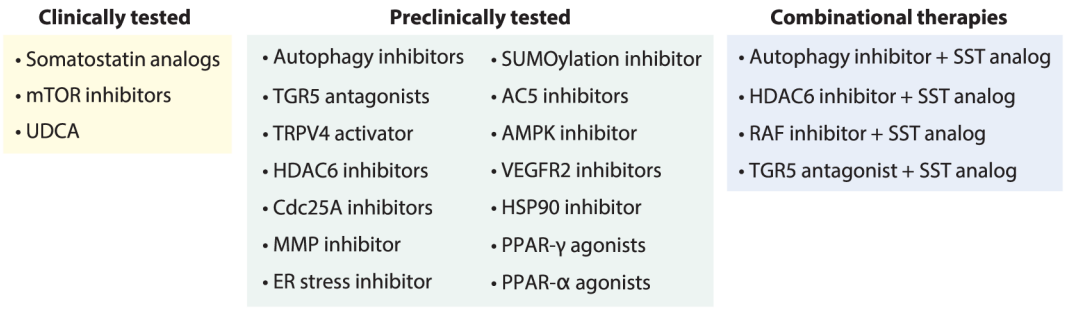


Figure 5.

Therapeutic interventions in PLD. Abbreviations: AC5, adenylyl cyclase 5; AMPK, AMP-activated protein kinase; Cdc25A, cell division cycle 25A; ER, endoplasmic reticulum; HDAC, histone deacetylase; HSP, heat shock protein; MMP, matrix metalloproteinase; mTOR, mammalian target of rapamycin; PLD, polycystic liver disease; PPAR peroxisome proliferator-activated receptor; RAF, rapidly accelerated fibrosarcoma; SST, somatostatin; SUMO, small ubiquitin-like modifier; TGR5, Takeda G protein–coupled receptor 5; TRPV, transient receptor potential vanilloid; UDCA, ursodeoxycholic acid; VEGFR, vascular endothelial growth factor receptor.