Emerging Therapies for Childhood Polycystic Kidney Disease

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Cystic kidney diseases comprise a varied collection of hereditary disorders, where renal cysts comprise a major element of their pleiotropic phenotype. In pediatric patients, the term polycystic kidney disease (PKD) commonly refers to two specific hereditary diseases, autosomal recessive polycystic kidney disease (ARPKD) and autosomal dominant polycystic kidney disease (ADPKD). Remarkable progress has been made in understanding the complex molecular and cellular mechanisms of renal cyst formation in ARPKD and ADPKD. One of the most important discoveries is that both the genes and products proteins of ARPKD and ADPKD interact in a complex network of genetic and functional interactions. These interactions and the shared phenotypic abnormalities of ARPKD and ADPKD, the “cystic phenotypes” suggest that many of the therapies developed and tested for ADPKD may be effective in ARPKD as well. Successful therapeutic interventions for childhood PKD will, therefore, be guided by knowledge of these molecular interactions, as well as a number of clinical parameters, such as the stage of the disease and the rate of disease progression.

Keywords: childhood PKD, therapy, tolvaptan, combination therapy, multi-kinase inhibitors

AUTOSOMAL RECESSIVE POLYCYSTIC KIDNEY DISEASE (ARPKD)

Autosomal recessive polycystic kidney disease (OMIM #263200) is characterized by renal cysts and hepatobiliary dysgenesis and is a substantial cause of morbidity and mortality in children (1, 2). ARPKD is caused by mutations in the PKHD1 gene which encodes a protein known as fibrocystin or polyductin (FPC), and both the gene and protein interact with the autosomal dominant polycystic kidney disease (ADPKD) genes and proteins.

AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE

Autosomal dominant polycystic kidney disease is one of the most common genetic disease affecting 1/400 to 1/1,000 individuals worldwide. ADPKD is generally a late-onset, systemic disease characterized by bilateral, progressive enlargement of focal cysts occurring in all nephron segments with variable extrarenal manifestations (3).

Autosomal dominant polycystic kidney disease was originally thought to be caused by mutations in two genes, PKD1 (on chromosome 16p13.3) (OMIM #173900) and PKD2 (on chromosome 4q21)
(OMIM #173910). These genes encode the protein polycystin 1 (PC1) and polycystin 2 (PC2), respectively.

There has always been a nagging suspicion that at least one additional disease-causing gene was as yet undiscovered because there has always been a small number of genetically unresolved families (GUR) that did not link to either locus (4–6). Recent reexamination of these GUR families demonstrated that mutations in GANAB (OMIM 104160) encoding the glucosidase II subunit α on chromosome 11q12.3 cause a mild form of ADPKD and autosomal dominant polycystic liver disease of varying severity, most likely due to defects in PC1 maturation (7).

Childhood ADPKD may be indistinguishable from ARPKD, and histological or genetic analysis may be necessary to differentiate the two (2, 8). The prevalence of pediatric patients with ADPKD in our polycystic kidney disease (PKD) clinic is approximately equivalent to the number of ARPKD patients, and both are significant sources of morbidity and mortality in children. The interaction between the genes, proteins, and overlapping cystic phenotypes suggests that therapeutic interventions and lessons learned from clinical trials in ADPKD can be applied to patients with ARPKD.

**PATHOPHYSIOLOGY AND TRANSLATIONAL IMPLICATIONS**

**Cellular Pathophysiology**

Cyst formation and progressive growth is a complex dynamic process with multiple interacting signaling components that all contribute to disease, but never act autonomously. The early investigations of PKD focused on fundamental phenotypic changes that would be necessary for a normal renal tubular epithelial cell to become a cystic epithelial cell. Normal renal epithelial cells changed from a mature, differentiated, non-proliferative, absorptive cell to a partially de-differentiated secretory cell characterized by specific polarity defects and increased rates of proliferation (9).

These led to the identification of a myriad of signaling molecules and signaling pathways that were found to be abnormal in cystic epithelium. Collectively, these changes define what is referred to as the "cystic phenotype." Figure 1 is a cartoon that includes some but not all of the aberrant signaling pathways that constitute this cystic phenotype. The precise mechanisms by

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**FIGURE 1** The cystic cellular phenotype. This cartoon is an abridged composite of the abnormal signal transduction pathways reported to be active in polycystic kidney disease (PKD). Two main conduits that lead to unchecked proliferation are (1) the EGFR axis (orange path) and (2) a G-protein axis (aqua blue path) that leads to increased cyclic adenosine monophosphate (cAMP) and a switch in phenotypic response of renal epithelia to cAMP. The pathways suggest the following: in autosomal recessive polycystic kidney disease (ARPKD), an apical EGFR results in the axis becoming active resulting in reciprocal phosphorylation of the non-receptor tyrosine kinase cSrc (purple); in autosomal dominant polycystic kidney disease (ADPKD), a mutated polycystin 1 (PC1) leads to increased amphiregulin, activating EGFR, resulting in increased cSrc phosphorylation; in both ARPKD and ADPKD, cSrc activity (purple) alters the cellular response of cAMP resulting in proliferation; in addition, in ADPKD the cytoplasmic tail, PC1-p30, is overexpressed leading to acSrc-dependent activation of STAT3 by tyrosine phosphorylation. EGFR and cAMP signaling amplify the activation of cSrc/STAT3 by PC1-p30. Targeting proliferation will always be a requirement to effectively slow the progression of PKD and prevent the need for renal replacement therapy. Targeting single molecules that bridge both pathways (such as cSrc) is a logical approach to get maximum effectiveness with minimal dosing, thereby limiting toxicity. Pharmacological inhibition with a single compound that targets multiple pathways (such as a multi-kinase inhibitor — tesetakinib) should provide a similar benefit. However, no single compound will provide lifetime effectiveness. Effective therapy will require multiple compounds administered in a disease stage-specific manner that will need to be individualized, accounting for variations in disease severity and rate of progression.
which mutated PKD proteins disrupt normal signaling and cause renal cyst are not entirely understood but significant progress in understanding the cellular events have been made.

In vitro and in vivo experimental models have been used to identify fundamental pathogenic features in human PKD and are thought to be pathogenic in both ARPKD and ADPKD. These include the following:

- aberrant intracellular levels of the second messenger, cyclic adenosine monophosphate (cAMP), coupled with decreased intracellular calcium increasing both proliferation and secretion;
- abnormalities in expression and localization of the ErbB or epidermal growth factor (EGFR)—family of receptors and ligands (EGFR axis), leading to increased proliferation;
- abnormal activity of cSrc (p60Src), a non-receptor tyrosine kinase that serves as a critical mediator of cross talk between the EGFR axis and G-protein-cAMP pathways. In addition, cSrc interactions with the cleaved C-terminal PC1 tail (PC1-p30) activate the transcription factor STAT3;
- activation of mammalian target of rapamycin (mTOR) signaling;
- alterations in cell–cell and cell–matrix interactions;
- changes in interstitial macrophages that leads to progressive interstitial fibrosis.

Clinical trials have to date been largely based on targeting these complex cellular signaling features of a cystic cell. Therefore, a brief discussion of each and the evidence supporting the pathogenic features listed above are included below. A brief discussion of the results of clinical trials to date will follow. A list of current and completed clinical trials can be found at http://clinicaltrials.gov.

**cAMP-Mediated Proliferation and Secretion**

The cAMP-dependent pathway is a G-protein-coupled receptor signaling pathway. Increased intracellular cAMP levels in a normal renal epithelial cell elicit a response that reduces MAPK activity resulting in a decreased rate of cellular proliferation. However, under conditions of low levels of intracellular calcium, a cSrc-dependent phosphorylation of β-Raf, allows the cell to bypass Raf-land increase ERK phosphorylation and subsequent cell proliferation (see Figure 1) (10, 11). This also changes the normally absorptive renal epithelia cell to a secretory renal epithelial cell which contributes significantly to the progressive enlargement of cysts in ADPKD (12).

Therapeutically, increased cAMP is reduced by vasopressin and concerns regarding potential hepatic injury. Tolvaptan is, therefore, not currently recommended for the treatment of childhood PKD.

**EGFR (ErbB) Axis**

An abundance of evidence demonstrates that the epidermal growth factor receptor (EGFR) and other ErbB receptors and their ligands (the EGFR axis) are important mediators of renal cystic epithelial proliferation in PKD. In human ADPKD and ARPKD and rodent models of PKD, renal cystic epithelia display overexpression and mislocalization of one or more ErbB receptors to the apical cell surface instead of the customary basolateral localization seen in the normal human kidneys (17–19). These apically expressed ErbB receptors are functional and capable of generating a proliferative signal in vitro (20). Preclinical studies have demonstrated that in vitro and in vivo inhibition of ErbB receptor tyrosine kinase activity with tyrosine kinase inhibitors (21, 22) or genetic manipulation (23) and/or reduced ErbB ligand availability (24) significantly reduced cyst formation and enlargement.

Recent studies have provided a direct link between PC1 and the ErbB ligand amphiregulin. Studies revealed that the promoter activity increased and established that cells with a mutated PC1, a reduced level of PC1, and primary cystic cells isolated from ADPKD kidneys exhibit increased amphiregulin expression (25, 26). In addition, microarray profiling of human ADPKD cells and a conditional mouse model (Cre;Pkd1(Cre-21,19)) found that ErbB4 activation was a major driver of cellular proliferation in ADPKD and may well be a biomarker of disease progression (27).

**cSrc**

cSrc is a critical intermediate that connects both the cyclic AMP and EGFR pathways and, therefore, plays a critical role in integrating signaling in normal and cystic epithelium. In ADPKD, PKD1 mutations give rise to increased production of amphiregulin that in turns activates (phosphorylates) the EGFR receptor resulting in a reciprocal phosphorylation (activation) of cSrc. Phosphorylated cSrc activates β-Raf, which alters the response of renal epithelia to cAMP from a normally antimitotic to a pro-proliferative phenotype. Additionally, activated cSrc interacts with PC1-p30, a proteolytic fragment of the PC1 cytoplasmic tail, resulting in STAT3 phosphorylation and further increased proliferation (28, 29). This cSrc-mediated activation of STAT 3 is augmented by increased activity of the EGFR axis and increased cAMP, thereby promoting even greater proliferation of tubular epithelium and cyst enlargement (29, 30).

These interactions forecast a pathologic proliferation pathway where mutated PC1 increases amphiregulin expression, resulting in activation of ErbB receptors and reciprocal phosphorylation of cSrc. Phosphorylated cSrc integrates and amplifies proliferative signals from EGFR and cAMP and together with the PC1 cytoplasmic tail, PC1-p30, activates STAT3 which leads to even further intensification of the proliferative signals (29).

1www.fda.gov/safety.
Bosutinib, a cSrc inhibitor, has undergone clinical trials in ADPKD. Although very effective in reducing total kidney volume, it did not effect changes in renal function.2

Mammalian Target of Rapamycin
The mTOR pathway integrates signals from growth factors (including EGFR), G-protein coupled receptors (which generate cAMP), cellular energy levels, nutrient status, and stress conditions to stimulate protein synthesis and cell growth through activation (phosphorylation) of S6K1 and eIF4E (31, 32). In human ADPKD and ARPKD and a variety of animal models, cyst-lining epithelium demonstrates increased activity of mTOR (32–35). The mTOR inhibitors rapamycin and everolimus have been tested in human clinical trials and were found to be ineffective in slowing total kidney volume or preventing loss of renal function (36, 37).

It is impossible to imagine how a single compound could provide lifetime effective therapy even if started early in the disease process. However, the identification of pathological cellular events provides a starting point for building future therapeutic interventional strategies for childhood PKD. Challenges including the focal nature of cyst formation and the large variation in the phenotypic expression of ARPKD and ADPKD are not trivial. The substantial intra-familial phenotypic variability seen in both ARPKD and ADPKD suggests that complex factors which influence or direct the timing and severity of disease are operative.

Molecular Pathophysiology
Improved molecular techniques and increased specificity in producing targeted gene mutations has allowed development of orthologous rodent models with conditional and hypomorphic mutations in Pkd1, Pkd2, and Pkhd1. Studies in such models which more accurately reflect the human disease have yielded unexpected results regarding mechanisms of cyst development and enlargement in PKD. Advances in sequencing, in concert with improved methods to produce animal models with specific mutations including those found in PKD patients, allow suspected mechanistic processes to be directly tested. These new insights along with lessons learned from the original clinical trials will lead to novel therapeutic interventions for PKD.

For example, in an intricate study, the genetic combination of five cystic disease models, including orthologous Pkd1, Pkd2, Pkhd1, and the two polycystic liver disease genes, Prkcs and Sec63, resulted in different combinations of mutant alleles which allowed the functional relationships between these genes to be defined (38). These combinations demonstrated that (1) Prkcs and Sec63 mutations result in impaired biogenesis of PC1; (2) PC1 dosage modifies the severity of both ADPKD and ARPDK; (3) the threshold level of PC1 necessary for normal tubular morphology varies by nephron segment with collecting ducts being most sensitive; and (4) overexpression of Pkd1 is capable of rescuing a mutant Pkhd1 animal (38).

Most if not all of the numerous cystic kidney disease proteins, including PC1, PC2, and FPC, are found in primary cilia or basal body of cilia which led to the cilia theory and the term “ciliopathies” to cover any disease caused by a mutation in a protein that is localized to the cilia (25, 39). PC1 and PC2 are predicted to form a complex on the primary cilium creating a mechanosensor that transmit external signals such as flow, to the renal epithelial cell (40, 41).

In a similar experiment as that described above, mouse models with tissue-specific and inducible knockouts of Pkd1 and Pkd2 alone or in combination with knockouts of cilia proteins Kif3a and Ifi20 revealed that: disruption of cilia reduced cyst growth caused by loss of PC1 or PC2; simultaneous loss of PCs and either Kif3a or Ifi20 resulted in milder disease severity than that seen when either PC protein was inactivated; and the length of time that intact cilia existed after the loss of PC’s increased disease severity (42). This suggests the existence of a cilia-dependent proliferative or cyst-promoting pathway that is inhibited by a normal PC1/PC2 complex (43).

The mechanosensing function of primary cilia was originally thought to result in increased calcium influx into the cell. In the absence of a normal PC1/PC2 channel, calcium levels in the cell fall and in the context of high cAMP levels, the cell phenotype becomes cystic. In a recent study, the primary cilia of multiple cell types including renal epithelial were shown not to transmit a calcium signal upon bending (44). The authors concluded that if cilia act as mechanosensor or a flow sensor, it does not occur through calcium signals.

The two-hit theory, proposed to explain the focal nature of cyst formation in PKD, stated that a somatic mutation or “second hit” in addition to the germ-line mutation was necessary for a cell to become cystic. Although this may explain some of the focal nature of cyst formation in ADPKD, other factors have been shown to influence disease progression and severity. On a cellular level, these include: the developmental timing of PKD1 inactivation (45, 46); reduction in functional PC1 dosage (38, 47, 48); differences in sensitivity to PC1 dosage (48); and the proximity effect, where a cystic cell or nephron creates a “snowball effect” triggering cyst development in neighboring cells or nephrons (49).

On a molecular level, a number of factors demonstrate that complex inheritance patterns influence disease severity in both ADPKD and ARPKD. These include hypomorphic or incompletely penetrant alleles (50); PKD1 or PKD2 homozygosity (47); compound heterozygosity (51); trans-heterozygosity (52); somatic and germ-line mosaicism (53); epigenetic regulators (54–57); genetic modifiers (58); co-inheritance of a PKD1 or PKD2 mutation and an additional cyst-causing gene such as HNF1β (59, 60) or the tuberous sclerosis 2 gene (61); and alternative splicing of Pkd1 that produces transcripts with distinct expression patterns and function (62).

Clinical Trials and Lesson Learned
The diagnosis of childhood PKD is no longer the terminal diagnosis as was once considered. For children with ARPKD, advances in neonatal critical care and renal replacement therapy have allowed many to survive much longer than what was possible just a few decades ago. Insights into the development and treatment of congenital hepatic fibrosis and portal hypertension, a complication

2http://ClinicalTrials.gov identifier NCT01233869.
the progression of PKD will be discovered and adherence or avoidance of such factors may slow the rate of progression and eliminate the need for pharmacological intervention or renal replacement therapy for some.

The importance of genetic dosage, modifier genes, and somatic mutations in the clinical course of PKD in an individual patient provide compelling rationale for a personalized medicine approach. Personalized medicine will mean tailored approaches that modulate functional gene dosage and consider not only individual genotypes but also account for the response of the kidney to the disease and the unanticipated response of the kidney to therapy. This unanticipated response to therapy may be active in tolvaptan therapy, where patients treated with Jineare© were reported to have increased urinary shedding of heparin-binding EGF-like growth factor (HB-EGF) (68). In ARPKD and ADPKD cysts, cystic epithelia express EGFR or ErbB receptors on the apical side (urinary side) of the cell. The presence of HB-EGF, a powerful mitogen, in the urine may stimulate these apical receptors prompting a proliferative signal that would counter at least some of the reduced proliferation gained by decreasing cAMP levels with tolvaptan therapy. This suggests that a tyrosine kinase inhibitor against EGFR or an enzyme inhibitor to prevent HB-EGF processing or both, added to tolvaptan therapy may lead to greater benefit especially in terms of reduced total kidney volume.

The progress made in understanding the pathophysiology of PKD has been remarkable and despite the work still remaining, patients and parents can take heart that two clinical trials for children with PKD are underway: one for children with ADPKD [Tolvaptan (NCT02964273) Belgium and Italy] and one recently approved for the use of multi-kinase inhibitor, TSV in children with ARPKD.

**AUTHOR CONTRIBUTIONS**

WS and EA contributed equally to the conception and design of the manuscript; drafted the article and made critical revisions related to the intellectual content of the manuscript; and approved the final version of the article to be published.

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