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Review

Polycystic kidney disease: Pathogenesis and potential therapies ☆

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ABSTRACT

Autosomal dominant polycystic kidney disease (ADPKD) is a prevalent, inherited condition for which there is currently no effective specific clinical therapy. The disease is characterized by the progressive development of fluid-filled cysts derived from renal tubular epithelial cells which gradually compress the parenchyma and compromise renal function. Current interests in the field focus on understanding and exploiting signaling mechanisms underlying disease pathogenesis as well as delineating the role of the primary cilium in cystogenesis. This review highlights the pathogenetic pathways underlying renal cyst formation as well as novel therapeutic targets for the treatment of PKD. This article is part of a Special Issue entitled: Polycystic Kidney Disease.

1. Introduction

On gross pathological examination, the polycystic kidney is impressive. The profound morphological disorganization of a tissue that is normally an exquisite exemplar of elegant design speaks to the magnitude of the cellular de-differentiation and dysregulation that can occur as a consequence of relatively small genetic alterations. Autosomal dominant polycystic kidney disease is fairly common, affecting between 1 in 500 and 1 in 1000 people. The disease is characterized by the slow development, over decades, of large fluid filled cysts in the kidneys. These cysts dramatically enlarge the kidneys and, more importantly, severely compromise the functional integrity of the remaining normal parenchyma. Clinically significant impairments of renal function will usually occur by late middle age. Roughly 50% of ADPKD patients will progress to end stage renal disease, requiring transplant or dialysis [1–3]. There is substantial variability in disease presentation, even within families. Although this heterogeneity can be explained by the variable nature of disease causing somatic mutations, modifier genes may also be inherited independently of the PKD mutation. These modifiers may include the angiotensin-1-converting enzyme (ACE) gene, the CFTR gene or the Tuberous Sclerosis Complex-2 gene, all of which may affect disease severity [4–9]. Although poor prognostic factors such as hypertension, early onset, male gender, increased kidney size and rate of growth, and microalbuminuria have been identified, the reasons for some of these apparent correlations are less well understood [10–17].

Most patients present with flank pain, hypertension, hematuria, renal insufficiency, and/or proteinuria. The flank pain may be secondary to calculi, renal hemorrhage, or be due to a urinary tract infection [2]. Renal function begins to decline in the fourth decade of life with the glomerular filtration rate (GFR) decreasing by 4.4 to 5.9 mL/min per year [1]. The decrease in GFR is inversely proportional to kidney size and cyst volume as assessed by the Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease (CRISP) [18–20]. Because ultrasound measurements cannot discern changes in kidney size over short time intervals, magnetic resonance imaging (MRI) with or without gadolinium has become the gold standard for assessing changes in kidney volume and thereby prognosis [21,22].

As there is no specific or targeted clinically approved therapy, current practice focuses on strict blood pressure control with ACE inhibition and the use of statins to reduce the associated cardiac mortality that coincides with chronic kidney disease [23]. Some patients experience abdominal and back pain from the enlarged kidneys and in these cases relief may be obtained via partial or total nephrectomy, or sclerosis of the cysts [24]. These procedures may also be required to accommodate an allograft. For those patients who progress to end stage renal disease, the options are limited to dialysis or renal transplantation. Hemodialysis is often preferred for technical ease in the setting of enlarged kidneys, and the outcomes of patients on dialysis are comparable to or better than those of non-ADPKD patients [25]. Mortality in patients with ADPKD is most often attributable to cardiac disease, infection, intracranial aneurysm, and hypertensive intracerebral hemorrhages [26].

Amongst ADPKD patients, 85–90% of cases result from mutations in PKD1, while another 10–15% of cases are accounted for by mutations in PKD2 [27]. There are also a small number of families with classic presentations of PKD whose members appear to have

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mutations at loci distinct from those of PKD1 and PKD2, suggesting that a third locus may be involved [28–30]. Patients with mutations in PKD1 experience a more severe phenotype, with one study reporting a median age of death or onset of end-stage renal disease of 54.3 years versus 74.0 years for patients with PKD2 mutations [31]. This discrepancy is hypothesized to result from increased cyst number, not size [32]. At present, over 300 truncating mutations of PKD1 and 91 mutations of PKD2 have been identified in patients with ADPKD. There are approximately another 100 disease-causing mutations which are missense [1]. Given this large database, molecular diagnostics are now becoming an option for situations when imaging studies are inconclusive, for when patients wish to know their genetic predisposition, or when the question of organ donation arises [33]. Interestingly, greater than 10% of patients come from families in which neither parent is affected [1].

PKD1 (polycystic kidney disease 1, ch16p13.3, 46 exons) encodes polycystin-1 (PC-1), a 462 kD, 4303 amino acid integral membrane protein with 11 transmembrane domains, a long extracellular N-terminus with multiple binding domains and a short cytoplasmic C-terminus that interacts with multiple proteins, including the protein product of PKD2 (polycystic kidney disease 2, ch4q21, 15 exons), polycystin-2 [3]. Polycystin-2 (PC-2) is a significantly smaller 110 kD protein with six transmembrane domains.

Both of the polycystin proteins exhibit complex subcellular localizations. Polycystin-1 is found in the basolateral plasma membrane domain of polarized epithelial cells, where it participates both in intercellular adherence junctions and in focal adhesion complexes with the underlying basement membrane [34]. In addition, a cleavage product of PC-1 that includes the C-terminal tail can translocate to the nucleus to regulate gene transcription [35,36]. Most of the polycystin-2 protein is concentrated in intracellular compartments, where it appears to play a role in regulating the release of calcium from intracellular stores. Its role as a cation channel is consistent with the fact that it is a member of the TRP family of ion channels [37]. PC-2 may also play a role in cellular proliferation and differentiation by controlling cell cycle regulation [38]. Both PC-1 and PC-2 are localized to the primary cilium that graces the apical surfaces of most polarized epithelial cell types. This non-motile, chemo- and mechano-sensory structure seems to be critically intertwined in the pathophysiology of renal cystic disease. Mutations in many genes that encode proteins involved in ciliary function lead to some manner of cystic disease [39,40].

While the exact physiological and pathological roles of these two proteins are still debated, it is clear that renal cystogenesis occurs when both copies of one or the other polycystin gene are either mutated or knocked out [41,42]. In mice, homozygous mutations of PKD1 and PKD2 result in embryonic lethality at E12.6–16.5 [42]. Heterozygous mice appear essentially phenotypically normal, occasionally developing a few hepatic and renal cysts later in life [43]. In addition, decreasing PKD1 expression is sufficient to cause cystic disease in mice [44] while overexpression of polycystin-1 in transgenic mice also results in renal cyst formation [45]. A study by Piontek et al. revealed that inactivation of PKD1 prior to postnatal day 13 in conditional knockout mice results in an extremely rapid disease course of cyst development, while inactivation after this developmental time point results in much milder disease progression [46,47]. These findings suggest that the polycystin proteins may function as important “brakes” on cell growth and division during renal development and that rapid proliferation of renal epithelial cells, such as occurs during renal development, may create an environment that facilitates the cellular consequences of polycystin mutation to become manifest. There is also evidence for a *trans*-heterozygous model of ADPKD, consistent with a two-hit hypothesis for disease initiation [48]. A third-hit model has also been proposed, in which renal injury stimulates the rapid cellular proliferation that, as noted above, may be a prerequisite for the cystic changes to occur after somatic mutagenesis or in association with reduced polycystin expression. This model may explain, at least in part, why disease initiation occurs so long after the initial genetic insult [49].

2. Introduction to the primary cilium: a rediscovered organelle

Eukaryotic cilia are microtubule-based structures that can be either motile or non-motile. Motile cilia are found in groups, lining large epithelial surfaces such as those of the trachea or cerebral ventricles, where they serve to clear mucus [50,51] or circulate cerebral spinal fluid [50,52,53], respectively. Non-motile or primary cilia, in contrast, are solitary, specialized ‘antennae’-like protrusions that extend markedly above the cell surface of nearly every cell in the vertebrate organism [54].

First described over 110 years ago, the exact function of these appendages in, or rather on, the cell remains elusive even today [55]. Because cilia project out and above the cell surface, they are currently thought to function in sensing and responding to the extracellular environment [56]. Structurally distinct from motile cilia, primary cilia have reappeared in the spotlight because recent data suggest these structures play important roles in photo-, chemo-, and mechanosensation [57]. Thus, the primary cilium may be structurally adapted to translate a variety of extracellular signals into intracellular signals. Furthermore, ciliary defects may be the common mechanism responsible for a heterogeneous group of disorders including renal cystic disease, retinal degeneration, anosmia (as in Bardet–Biedl syndrome), situs inversus, and neural tube defects [54,58,59].

Dividing cells are thought to be incapable of cilium formation because the basal body (one of the cell's centrioles) is required for the assembly of the mitotic apparatus [60,61]. Therefore, ciliogenesis is expected to occur when cells have entered mitotic quiescence [62,63]. Conversely, the presence of the cilium may in itself act to prevent cell division, since the basal body centriole is not available for the formation of the mitotic spindle. Thus, regulated ciliary disassembly may be an important factor in controlling proliferation, and perturbations in cilia formation might be expected to lead to hyperproliferative states.

3. Primarily cilium structure and function

As early as 1962, Sorokin et al. attempted to explain the differences in development between primary cilia and motile cilia [64]. Motile cilia have a $9+2$ arrangement, with a pair of singlet microtubules in the center, connected by radial spokes to nine doublets in the periphery. In contrast, primary cilia have a $9+0$ microtubule arrangement with nine doublets along the periphery [65]. Although contiguous with the apical membrane, the ciliary membrane's lipid and protein composition is distinct [66]. Moreover, at the transition point from the plasma membrane to the ciliary membrane, the triplet microtubules of the basal body centriole transform into double microtubules within the ciliary axoneme [67].

The first steps in ciliation involve the modification and movement of the designated centriole to a position below the apical membrane [68]. In the G1 phase of cell division, each cell contains one centriole (mother centriole) that acts as a template for the assembly of the other centriole (daughter centriole). Although structurally indistinguishable, it is always the mother centriole that serves as both the microtubule organizing center and the core structure of the basal body [69].

At the base of the primary cilium lies the basal body, which is the mother centriole, modified to include transition fibers, basal feet, and rootlets. The transition fibers of the basal body connect the microtubules to the plasma membrane [70]. Appearing like ‘pinwheels’ in cross-section, these structures are may participate in

regulating protein trafficking into and out of the cilium. Deane et al. have suggested that transition fibers could serve as docking platforms for molecules involved in cilium construction as well as for ciliary cargo [71]. Basal feet are lateral projections below the transition fibers and most likely connect the microtubules in the cytoplasm to the base of the cilium. Finally, ciliary rootlets extend from the basal body deep into the cell, and may even contact the Golgi apparatus [72]. Most likely these rootlets act like tentacles that penetrate the cell to secure a foundation for the cilium. However, it is also conceivable, given the connections with the Golgi apparatus, that these rootlets allow for selective transport of cargo directly to the ciliary membrane. In effect, the structures of the basal body may be important not only for maintaining ciliary structure, but also for selecting and targeting proteins to the ciliary membrane.

All of the proteins required for ciliary assembly, sensation, and signaling must be transported from within the cell to the very tip of the cilium, as cilia lack ribosomes. A microtubule based "conveyer belt" shuttles proteins along the ciliary axoneme in a process known as intraflagellar transport (IFT) [73]. IFT was initially discovered in the green algae *Chlamydomonas* and has since been found to occur in other ciliated eukaryotes [74–76]. In this process, proteins gather into IFT particles at the base of the cilium and these particles are then transported up the cilia via kinesin motors and downwards via a dynein motor protein. The importance of this process in the context of the present discussion of renal cystic disease is highlighted by the consequences that result from the kidney-specific inactivation of the gene encoding the Kif3a subunit of kinesin-II in mice. This genetic manipulation results in the absence of cilia in affected nephron epithelial cells. In addition, these mice develop severe renal cystic disease that resembles the pathology associated with PKD [77]. Using IFT, the cell can deliver important structural and signaling molecules into the cilium and, as a consequence, the cilium can transmit information regarding the external milieu back to the cell [78,79].

4. Ciliopathies and renal cystic disease

In recent years, considerable interest has developed in the primary cilium as a locale for proteins involved in renal cystogenesis. One of the first discoveries that associated the primary cilium to cystic disease involved the demonstration that the Tg737 gene, whose function was disrupted in the Oak Ridge Polycystic Kidney mouse (Tg737*orpk*) [80], was in fact an ortholog of the *Chlamydomonas* Intraflagellar Transport Protein 88 (IFT88) [81]. Although the IFT88 mutant mice were already known to have developmental defects including cystic kidneys, the suggestion that a gene involved in ciliary assembly could cause such defects was new and important [82].

GFP-tagged versions of the mammalian polycystin-1 and polycystin-2 orthologs were localized to the ciliated tips of *Caenorhabditis elegans* male sensory neurons, and subsequently both polycystins were co-localized with the primary cilium in human and mouse kidney cell lines [83–85]. Interestingly, in addition to the polycystins, the protein responsible for ARPKD, fibrocystin, and the proteins responsible for the recessively inherited nephronophtheses, also co-localize with the cilium or the basal body [86–88]. Ciliary polycystins may play a part in coordinating a cellular response to changes in extracellular fluid flow. Praetorius and Spring have demonstrated that ciliary bending triggered by fluid flow results in an increase in intracellular calcium suggesting that the primary cilium may function as a mechanosensor [79,89,90]. It has been suggested that polycystin-1 and polycystin-2 may mediate this process, at least in part, by forming a mechanosensory complex that responds to shear stress by increasing cytoplasmic calcium [91–94]. Alternatively, or in addition, the polycystins may be responsible for governing cellular processes via the JAK/STAT [36,95], p53 [96], mTOR [97], NFAT/AP-1 [98] or Wnt signaling pathways [35,36,99]. If the polycystins are mutated, then presumably one or more of these cellular signaling functions are compromised, and cystogenesis ensues.

Proteins involved in key developmental signaling pathways, including those of the Wnt, hedgehog, and planar cell polarity pathways, are physically located in the cilium, lending further support to the hypothesis that this structure is somehow regulating proliferation by sensing the extracellular environment [100–104]. In addition to ADPKD, ARPKD and the nephronophtheses, a large number of syndromes, including Bardet–Biedl syndrome (in which patients have both renal cystic disease and anosmia), Kartagener's syndrome, Meckel–Gruber Syndrome, Joubert syndrome and Oro-facial-digital type 1, syndrome have been recognized to be associated with abnormal ciliogenesis or with disease-specific proteins that co-localize with cilia [105]. As more and more proteins are linked to the primary cilium, the list of these ciliopathies will doubtlessly continue to grow.

5. Mechanism of cyst growth — fluid secretion

Examined at a more macroscopic level, cysts originate as dilatations in the walls of intact tubules, initially filling from fluid filtered in the glomerulus [106]. However, as the cysts enlarge, they lose their connections to the parent nephron [106]. It is unclear what event(s) initiate cyst formation in ADPKD or what factors determine cyst localization along the nephron, although there is clearly an association with genetic predispositions that result in either abnormal cellular differentiation or maturation [106–108]. These abnormal cellular responses are hypothesized to arise, at least in part, from abnormal cilium formation [107,109], abnormal protein targeting [85,110], cyclic AMP activation [106,111,112], and unregulated cell proliferation and growth [113–116].

The pathological processes that facilitate cyst enlargement, however, are hypothesized to result from two specific cellular abnormalities: 1) increased fluid secretion into the cyst lumen and 2) inappropriately increased cell division of the cyst lining epithelium. The increased secretion might be expected to increase the hydrostatic pressure inside the cyst and encourage expansion, while the increase in cell proliferation would simultaneously induce *de novo* cyst formation. Grantham et al. have demonstrated that the rate of fluid secretion into the cyst lumen is directly proportional to the amount of the CFTR chloride channel present in the apical membrane. These data are consistent with the role for fluid secretion in driving cyst growth [117]. The epithelial cells that line the nephron normally function to drive the net absorption of fluid and electrolytes. *In vitro* estimates of cyst fluid production by PKD cells range from 26 to 475 ml per year [118]. Thus, PKD can be thought of, at least in part, as a disease in which the normally absorptive cells of the renal tubule adopt a largely secretory phenotype.

In the prevailing physiological model for fluid secretion by renal cyst epithelia cells, the Na,K-ATPase in the basolateral membrane mediates sodium extrusion in exchange for potassium uptake. Sodium re-enters the cell via a basolateral isoform of the sodium–potassium chloride cotransporter (NKCC1), which drives secondary active basolateral chloride entry. This chloride exits apically via the CFTR channel, driven by the electrochemical gradient for chloride across the apical membrane. The chloride flux drives paracellular sodium and water movement, thus promoting fluid accumulation within the cyst lumen [119]. A basolateral potassium channel is also required in order to allow egress of potassium that enters via the Na,K-ATPase and NKCC1 [120]. It is interesting to note that within the small cohort of patients that suffer from both cystic fibrosis and PKD, the PKD progression is slower than average, presumably because the mutated CFTR channel is unable participate in fluid secretion into the cysts [121]. The evidence for CFTR acting as a significant contributor to cyst growth has inspired pre-clinical trials of CFTR-inhibitors in animal models of PKD [122,123].

The CFTR chloride channel is activated by elevations in cytosolic levels of cAMP [124]. A large body of research indicates that cytosolic cAMP levels are elevated in renal cyst epithelial cells, perhaps as a consequence of the presence of autocrine or paracrine factors secreted into cyst lumens [111]. In addition, cAMP appears to constitute a powerful mitogenic stimulus for cyst epithelial cells [125,126]. Thus, both of the major phenotypic perturbations exhibited by ADPKD epithelial cells—excessive proliferation and fluid secretion—may be under the control of inappropriately elevated levels of cAMP.

6. Potential therapies for polycystic kidney disease

Recent advances in the understanding of pathways governing renal cystogenesis have led to a number of intriguing possibilities for therapeutic intervention. Some pathways target fluid secretion, while others target cellular growth and proliferation. cAMP was one of the first molecules implicated in the hyper-secretory phenotype of cyst formation that has been targeted by specific therapeutic interventions. Increased cAMP levels are a common feature of most models of PKD [127–129]. cAMP is also involved in the stimulation of the MAPK/ERK signaling pathway via Src and Ras [130]. Although the precise mechanism underlying the increase in cAMP is not known, it has been noted that vasopressin levels are increased in human ADPKD [131]. Upregulation of the vasopressin V2 (V2) receptor is also found in the cpk, pcy, and PKD2(WS25/−) mouse models, and PCK rat model of cystic disease [127,128,132]. The V2 receptor stimulates cAMP accumulation. Blockers of the V2 receptor have produced impressive therapeutic effects in animal models of cystic disease [127]. In addition, activating the somatostatin receptor reduces cellular cAMP levels, and somatostatin analogues have also produced promising results in human trials [133]. Ongoing clinical trials are currently evaluating the efficacy of the V2 receptor antagonist, tolvaptan, and long-acting somatostatins [134,135]. Other potential therapies that are directed at addressing fluid secretion include CFTR inhibitors and KCa3.1 inhibitors, which inhibit the basolateral potassium channel necessary for cAMP-dependent chloride secretion [120,136].

Although the pathways governing proliferation are complex and somewhat intertwined, a number of potential therapies have emerged that specifically target upregulated pathways. Given the parallels between the hyper-proliferative phenotype of PKD and the unregulated cell division in neoplasia, several chemotherapeutic agents have been explored in efforts to decrease cyst growth. These therapies include paclitaxel, epidermal growth factor receptor (EGFR) tyrosine kinase inhibition, TNF-α converting enzyme inhibition, and c-SRC inhibition [137,138]. While some of these agents have produced impressive results in animal models, it is important to note that these anti-mitotic agents must be tolerated over a patient's entire lifetime in order to be useful as a therapy for ADPKD, as it is likely that cyst growth will resume as soon as inhibition of proliferation is removed.

Several interesting potential target molecules for drug therapies have been found to be upregulated specifically in PKD. Efforts to exploit some of these potential targets have explored agents directed at CyclinD [139], B-raf [140], and mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK) kinase [141]. Intriguingly, it has also been shown that mammalian Target of Rapamycin (mTOR) activity is elevated in models of PKD [142]. mTOR is a serine/threonine kinase that regulates cell growth and proliferation, as well as transcription and protein synthesis. Shillingford et al. have reported that mTOR is regulated by polycystin-1 [97]. Rapamycin, also known as sirolimus, binds to FK506-binding protein (FKBP) and this complex then binds to and inhibits mTOR's kinase activity [143,144]. Indeed, treatment with rapamycin has been shown to improve renal cystic indices in the orpk and Tg737 rescue models for cystic kidney disease as well as the Han:SPRD rat model of ADPKD [97,142,145]. Unfortunately, recent Phase II trials of the utility of mTOR inhibitors such as everolimus and sirolimus for the treatment of PKD did not indicate substantial therapeutic efficacy [146–148]. Efforts are also being made to inhibit mTOR signaling less directly and perhaps with less toxicity through agents that produce TNF-α inhibition or through AMPK stimulation via metformin [149].

Investigators have used MEK inhibitors to diminish proliferation induced by MAPK/ERK signaling, which results from ligands present in cyst fluid that bind to and activate tyrosine kinase receptors [141]. Further down this pathway, Bukanov et al. have posited roscovitine, a cyclin-dependent kinase (CDK) inhibitor, as another potential therapy for human patients, given its relatively low adverse side effect profile [139,150]. Inhibition of the synthesis of glucosylceramide produces dramatic therapeutic effects in mouse models of ADPKD, [151] although the cellular mechanisms responsible for this effect remain to be thoroughly elucidated. Finally, histone deacetylases have emerged as promising targets that may be exploited for ADPKD therapeutic development [152,153].

7. Conclusion

Renal cystogenesis is characterized by the pathologic accumulation of fluid in epithelium lined cavities leading to the destruction of adjacent normal parenchyma. Inherited cystic diseases, including the most prevalent form, ADPKD, are hypothesized to result from abnormalities in proteins required for the proper formation and function of primary, nonmotile cilia in epithelial renal tubules. Although disruptions in cilia formation or mutations in proteins that co-localize with the cilium are associated with renal cyst development, the exact relationship between cystogenesis and ciliogenesis is unclear. Our incomplete understanding of cyst pathogenesis has hampered the development of specific clinical therapies. At present, there are no FDA-approved therapies for the treatment of PKD, and patients who progress to end-stage renal disease require renal replacement therapy. Recent research has suggested a number of promising target molecules and pathways, and extensive efforts are underway to explore and exploit these new avenues.

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