

Chapter 15

Autosomal Dominant Polycystic Kidney Disease Induced by Ciliary Defects

Jong Hoon Park, Yu Mi Woo, Je Yeong Ko, Do Yeon Kim

Department of Biological Science, Sookmyung Women's University, Seoul, 04310,
Republic of Korea

Author for Correspondence: Jong Hoon Park, PhD, Department of Biological Science,
Sookmyung Women's University, Chengpa-ro 47-gil 100, Youngsan-gu, Seoul, 04310,
Republic of Korea, parkjh@sm.ac.kr

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Abstract

Autosomal dominant polycystic kidney disease (ADPKD) is a common genetic renal disease, which is caused by pathogenic mutations of either PKD1 (85%) or PKD2 (15%) genes, encoding for polycystin-1 (PC1) or polycystin-2 (PC2), respectively. These two proteins hetero-dimerize in renal primary cilia to act as a calcium channel. Primary cilia that protrude from cell membranes have a microtubule-based finger-like structure and are found on most mammalian cells. Primary cilia in the kidney have no motility but act as mechanosensors to sense fluid flow through renal tubules. In addition, various signaling

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proteins related to Hedgehog (Hh) and platelet-derived growth factor receptor alpha (PDGFR α) are localized to the cilia to detect changes in the extracellular environment. Recent studies have demonstrated that many ADPKD animal models have defective cilia in the epithelial cells that line the cysts. Also, animal models targeting ciliary genes show abnormal phenotypes such as polycystic kidneys and developmental defects. These findings reveal that ciliary malfunction is sufficient to cause ADPKD. In this chapter, we will review the putative roles of cilia in cyst formation and development in ADPKD.

Key words: ADPKD; Cilia; Ciliopathies; PKD1; PKD2

Introduction

Polycystic kidney disease (PKD) is a group of inherited kidney disorders that induce bilateral cyst development in the kidneys. PKD is classified into two types: autosomal dominant (AD) and autosomal recessive (AR). ADPKD is estimated to have a prevalence rate of 1:400-1:1000 worldwide (1). ARPKD is estimated to have a prevalence rate of 1:10,000-1:20,000 (2). ADPKD is the most common case of PKD and occurs in middle age, whereas ARPKD is the most lethal form and even affects children (2). One of the prominent characteristics of ADPKD is the development of fluid-filled cysts induced by an abnormal cell proliferation of epithelial cells in both kidneys, followed by inflammation and fibrosis leading to chronic kidney failure. Despite the clinical significance of this disease, no effective treatments are currently available. Mutations in the polycystin genes, PKD1 and PKD2, are responsible for ADPKD. These proteins are located in the primary cilia of tubular cells. The discovery of several mutated proteins in human and murine ADPKD indicates that there is a tight correlation between primary cilia and cyst formation, cell polarity, STAT6 and mammalian target of rapamycin (mTOR) signaling (3). Understanding the relationship between ADPKD pathogenesis and ciliary defects will provide novel insights to develop specific therapeutic targets against ADPKD.

Autosomal dominant polycystic kidney disease (ADPKD)

ADPKD is the fourth leading cause of renal failure worldwide in adults and affects approximately 1 in 400 to 1 in 1000 people (1, 4). ADPKD is a multisystem disease characterized by numerous cysts and fluid secretions into the lumen in the bilateral kidney (5). In general, patients affected with ADPKD suffer from hypertension and other cardiovascular symptoms beginning in their twenties and grow lots of fluid-filled cysts by middle age, finally leading to end-stage renal disease (ESRD) in ~50% of cases, which requires dialysis or transplantation (4).

The pathophysiology of ADPKD is caused by mutations in the genes of PKD1 (chromosome region 16p13.3; approximately 85% of cases) or PKD2 (4q21; approximately 15% of cases), which encode the proteins polycystin-1 (PC1) and polycystic-2 (PC2), respectively. Mutation in PKD1 is associated with a more severe renal cystic disease than mutations in PKD2 (6). PC1 is a 450-kD protein with a large extracellular N terminus, 11 membrane-spanning domains, and a shorter cytoplasmic C terminus (7) and is associated with cell-cell and cell-matrix interactions at tight junctions, adhesions junctions, desmosomes, and focal adhesions (8). PC2 is a 968-amino acid protein that has six transmembrane domains with intracellular N and C termini (9). PC1 and PC2 proteins are known to form a complex that plays a role as a transient receptor potential channel involved in the regulation of intracellular calcium homeostasis (10, 11). This complex is localized to the primary cilium (12) and the endoplasmic reticulum (ER) (13), where it affects calcium concentrations in several subcellular compartments (14, 15). In the primary cilium, the PC1-PC2 complex may play a role as a mechanoreceptor to induce the influx of extracellular calcium in response to fluid shear stress (16, 17), while in the ER, it interacts with the ryanodine receptor and plays a role as a calcium release channel (18). Although the mechanisms are unclear, the loss of the functional PC1-PC2 complex leads to phenotype alterations such as the inability to maintain planar cell polarity, an imbalance between cell proliferation and apoptosis, increased fluid secretion, and remodeling of the extracellular matrix. The major signaling pathways associated with these phenotypic alterations include the intracellular deregulation of calcium homeostasis, cAMP accumulation and activation of protein kinase A (PKA), activation of mitogen-activated protein and mammalian target of rapamycin (mTOR) kinases, canonical Wnt signaling, and other intracellular signaling mechanisms (19, 20).

The most important abnormalities that occur in the tubular epithelium lining the cysts have been extensively described: disturbance in the balance between tubular cell proliferation and apoptosis, alterations in the polarity of membrane proteins, abnormalities of cell-matrix interactions, abnormal fluid secretion, and abnormal ciliary function (21).

At first, in ADPKD, abnormal proliferation in tubular epithelial cells is strongly associated with cyst development and/or growth. The process of cyst formation requires proliferative expansion of the epithelial lining of the collecting duct or renal tubules (22). Actually, increased proliferation was observed in early cysts or dilated tubules from human ADPKD specimens and some mouse models of sporadic ADPKD (23, 24). Increased apoptosis as well as cell proliferation is detected in kidney tissues with ADPKD. Although the precise pathways linking proliferation and apoptosis in ADPKD remain to be elucidated, there is some evidence that apoptosis plays a crucial role in cystogenesis: (1) tubular epithelial cell apoptosis is observed in most animal models of

PKD and in kidneys from patients with ADPKD; (2) induction of apoptosis in renal tubular cells leads to cyst formation *in vitro*; (3) abnormal increase in both proliferation and apoptosis occurs in cystic and non-cystic epithelial cells in the early stages of ADPKD; (4) caspase inhibition may induce less proliferation and apoptosis in tubular epithelial cells, leading to reduced cyst formation and kidney failure (25). Intriguingly, dysregulation of apoptosis plausibly induces cystic remodeling of renal tissue in cooperation with increased proliferation of tubular cells with disrupted planar cell polarity (PCP) and disoriented mitotic spindles (26).

The PCP pathway, which is necessary for oriented cell division and the establishment/maintenance of kidney tubule structure, is involved in ADPKD pathogenesis even though it is incompletely understood (27). In addition, cell-cell/cell-matrix interactions, which are mediated by integrin receptors, have long been associated with ADPKD but remain firmly understudied. Overexpression of extracellular matrix (ECM) proteins has been observed in human ADPKD cells and ADPKD animal models. In addition, the cysts lining epithelial cells show elevated adhesiveness to type I and type IV collagen in response to growth factors (28).

Fluid secretion is an important pathogenic mechanism of cyst development in ADPKD. A large number of cystic lesions exhibit loss of afferent and efferent tubule connections, which implies that cysts derived from tubular segments are disconnected from the glomerular filtrate. Therefore, net transepithelial fluid secretion is required for the expansion of cystic lesions (29). Fluid accumulation causes cyst enlargement due to swelling and stretching in the cells to stimulate cellular division (30). Cystic fibrosis transmembrane conductance regulator (CFTR) is a cAMP-regulated chloride channel expressed in the apical membranes of many secretory epithelia.

Finally, renal cilia are microtubule-based and play a role as mechanosensors in response to fluid flow. The mechanosensory function of cilia is lost with mutated PC1 proteins in renal tubular cells (16) and the loss of polycystin function is mostly linked with cilia, leading to abnormal calcium signals in response to fluid flow (3).

Primary cilia

Structure of cilia

Cilia and flagella are hair-like organelles found on eukaryotic cells when the cells were growth arrested or differentiated. These organelles project from the apical membrane of

epithelial cells. Although cilia were discovered in the 17th century, only motile cilia were studied for a long time, for example, in the respiratory epithelia that mediate airway clearance (3, 31). Relatively recent studies have focused on the structure and functions of primary cilia.

Cilia and flagella are identified by their structures. Although the outer membranes of cilia and flagella are lipid bilayer membranes that coincide with the plasma membrane of the cell body, receptors and other proteins involved in signaling are embedded in the outer membrane of cilia (32). The inside structures of cilia and flagella are comprised of a microtubule-based cytoskeleton known as axoneme, which is a cylindrical pole regulated by the assembly or disassembly of ciliary protein. The axoneme grows outward from the basal body, which is a modified form of centrioles for developing axonemes in cell-cycle arrested cells. The centrosome is a complex of two centrioles and functions as the main microtubule-organizing center (MTOC) (33). The core axoneme is comprised of nine outer doublet microtubules (9+0) that emanate from the triplet microtubules of the mother centriole in the basal body (34). The change in the microtubule structures occurs in the region where the microtubule attaches to the membrane, known as the transition zone. The transition zone has transitional fibers that emerge from the end of the basal body and function as linkers from the doublet microtubules to the ciliary membrane (35, 36). The ciliary or outer membrane particles are separated in the transition zone. Selected ciliary particles move to the ciliary compartment and the membrane associated protein particles are lined up in the region known as the 'ciliary necklace' (37, 38).

Most motile cilia contain an additional pair of central microtubules and axoneme-associated dynein arms as well as radial spokes for ciliary motility (36). Recent studies, however, found some motile cilia with '9+0' or '9+4' microtubule structures (39). The non-motile cilia also known as 'primary cilia' are comprised of nine outer doublet microtubules, but lack a pair of microtubules and other proteins involved in motility (Figure 1). Instead of motility, primary cilia function as 'sensory antennas'. The ciliary membrane contains a subset of receptors and ion channels that induce primary ciliary signaling pathways including phototransduction, olfactory sensing, mechanosensing, extracellular signaling including Hedgehog (Hh), Wnt, Platelet derived growth factor (PDGF) ligand, and planar cell polarity (PCP). Many organs and tissues in the mammalian body such as the brain, kidney, liver, pancreas and oviduct as well as olfactory and visual organs also have non-motile, primary cilia that detect and transmit signals from the external environment (32, 40, 41).

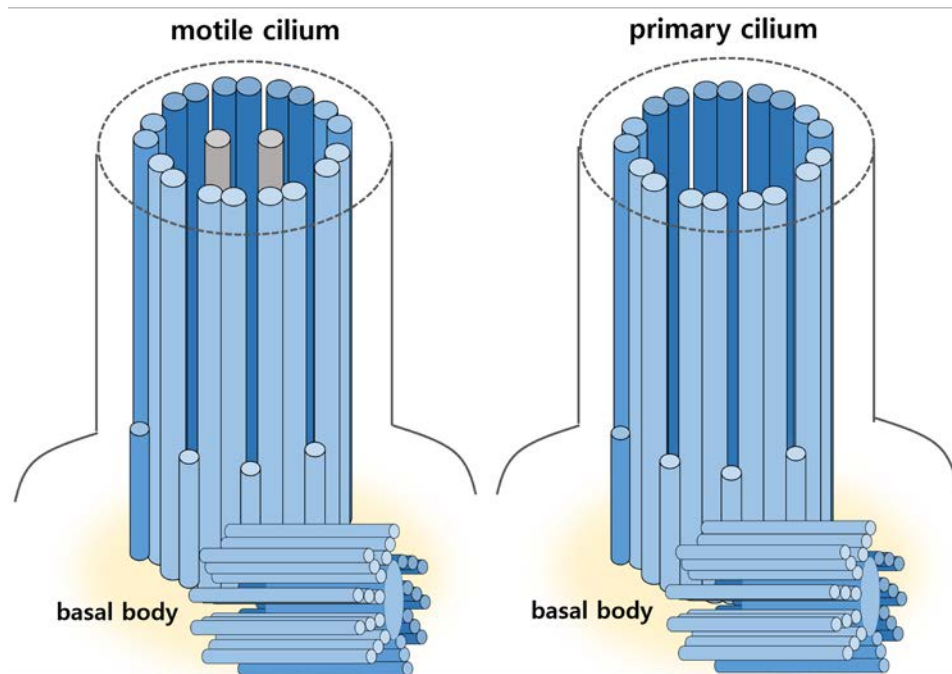


Figure 1. Structure of motile cilia and primary cilia. The inside structure of motile cilia is 9+2, and primary cilia is 9+0 microtubules based on the cytoskeleton, called the axoneme, which is a cylindrical pole regulated by the assembly or disassembly of ciliary protein. The doublet microtubule emanates from the basal body, which is a modified form of centrioles in cell-cycle arrested cells, ultimately resulting in assembly of the cilia.

Cilia and cell cycle

The cilia originate from the triplet microtubules of the basal body during interphase of cell division. The basal body is known as the centriole in metaphase of cell division. The centriole plays a role in determining the position of a dense matrix, called pericentriolar material, which in turn functions in organization of the microtubule during cell division (42). Because of basal body (centriole), formation of primary cilia also closely related with cell cycle regulation. Cilia are resorbed before S phase or during G2 (43) (Figure 2). When Golgi-derived (primary) vesicle attach to the mother centriole in the phase of G1, assembly of primary cilia begins. Additional Golgi-vesicles transport axonemal subunits at the mother centriole, and then accessory structures that induce docking and attachment of the mother centriole to the apical plasma membrane are formed (44, 45). Since docking of the mother centriole, axonemal subunits add to ciliary axoneme, and it leads to assemble and elongate primary cilia (35).

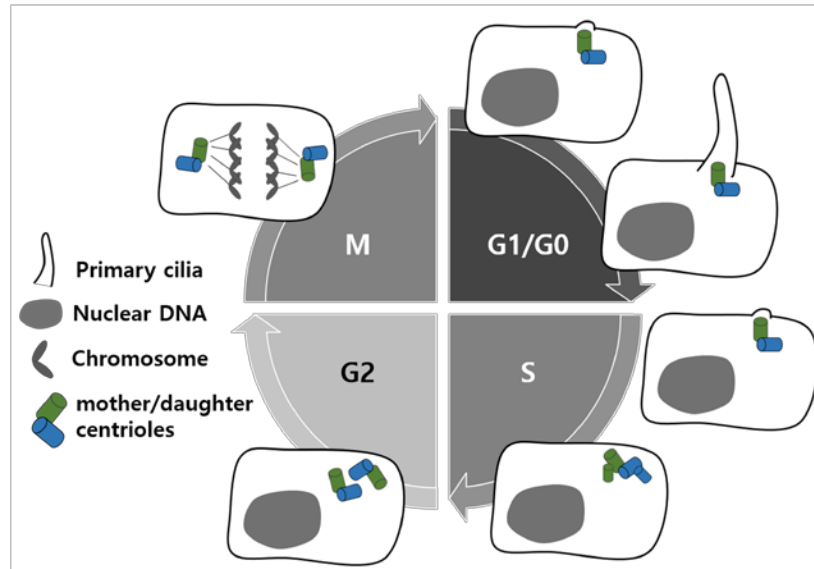


Figure 2. Regulation of primary cilia formation during the cell cycle progression. During the G1 phase, centrioles dock to the apical region of the cells to prepare for cilia formation. If cells enter the G0 phase, assembly of the primary cilia is induced. During the S/G2 phase, centriole duplication and cilia absorption/disassembly occur, leading to cell division. When progression of the cell cycle is complete, two daughter cells re-enter the G1 phase and prepare for cilia re-assembly.

Assembly of cilia

A number of components for cilia assembly have to be transported by ciliary precursors. Ciliary precursors were not described until 20 years ago, however, intraflagellar transport (IFT) was first discovered in *Chlamydomonas*, a unicellular green alga, by Rosenbaum and his colleagues (35, 46). They observed that IFT ascended and descended between the distal end of the flagella and the basal body along the ciliary axoneme (46). IFT was induced by large protein complexes known as complex A and B according to the direction of movement. Particles of IFT complex B function in anterograde IFT to the distal end of the cilia for ciliary assembly, whereas particles of IFT complex A are associated with retrograde IFT to the basal body during ciliary disassembly (47, 48). Anterograde or retrograde movement requires two classes of motor proteins, kinesins and dyneins, which gain energy by ATP hydrolysis. Heterodimeric kinesin-2 motors (Kif3a, Kif3b, KAP complex in mammals) accumulate IFT complex B (anterograde IFT) particles and transport them toward the tip of the cilia. Cytoplasmic dynein 1b (DHC2 in mammals) carries IFT complex

A particles (retrograde IFT) from the tip to the base (49-51). Recent studies reported that kinesin-2 motors congregate with not only IFT particles but also associated cargoes such as axonemes precursors, signaling molecules and retrograde motors, resulting in anterograde assembly in the cilia. Cytoplasmic dyneins, in contrast, restore kinesin motor proteins and IFT particles to the basal body (34).

Ciliopathies

Cilia were previously regarded as no more than small organelles. Following increased interest in cilia, however, studies have focused on disruptions in the cilia. Ciliary dysfunctions are related to multiple human genetic diseases called ciliopathies (52). The first study observed some developmental defects in Oak Ridge Polycystic Kidney mouse (ORPK mouse, mutation in IFT88) including cystic kidneys (32, 53). Later studies demonstrated that IFT88 was responsible for the assembly of the cilia and for abnormal cilia in the Tg737/ift88 mutant mouse (32, 42, 54). The importance of cilia in renal cystogenesis was revealed by knock-down of KIF3a (IFT-associated kinesin motor) in mouse kidneys (55). Altogether, loss of cilia or polycystin, which disrupted ciliary signaling, resulted in cystic disease. Recent data indicated that the timing of cilia defects determine the severity of the cystogenetic phenotype (56).

PKD and ciliary defects

Among the known ciliopathies, PKD is one of the most common renal genetic disorders. Recent studies have demonstrated that mutations in ciliary genes are closely related to the onset of cystic kidneys (12). Therefore, cilia-defective mouse models were produced to elucidate the function of renal cilia in the kidney. Most mouse models targeted by ciliary proteins showed embryonic lethality with multiple developmental defects (57-59). Consequently, many research groups have produced ciliary gene-targeted mice using kidney specific Cre mice (54, 57, 60). In this chapter, the phenotypes of renal cilia and aberrant signaling pathways in PKD mouse models targeted by ciliary genes are introduced.

Phenotype of renal cilia in representative PKD mouse models

According to many papers published so far, proteins related to the onset of PKD are localized to the cilia or basal body and regulate ciliary functions as well as the structure of the cilia (12, 61). The PC1 and PC2 proteins, encoded respectively by PKD1 and PKD2 genes, are localized to renal cilia. DeCaen et al. suggest that these two protein complexes

act as calcium channels in the primary cilia (62, 63) and regulate various intracellular signaling pathways associated with cell proliferation (64). Kidney-specific inactivation of *Pkd1* in the mouse results in the severe polycystic kidney phenotype (65), but there are no significant changes in the renal cilia (56, 65). However, a knockin mouse model targeted by pathogenic mutation of PKD1 (PKD1 p.R3277C) shows progressive PKD phenotype with elongated cilia of the renal collecting duct cells (66). These results indicate that the function and structure of renal cilia are regulated according to the type of genetic mutation of PKD1. The first mouse model to demonstrate that defects in renal cilia are associated with the development of PKD was the ORPK mouse model. The ORPK mouse is produced by insertion mutation of the *Ift88* (*Tg737*) gene related to ciliary assembly (54). This mouse model has the polycystic kidney phenotype with shortened renal cilia that accumulate with PC2 protein (53, 67). As the volume of papers on the relevance of ciliary defects and PKD has increased, various mouse models targeted by ciliary genes have been produced.

Many research groups have proposed that deficiency in the renal cilia is the driving force for PKD development. In this section, representative PKD mouse models targeted by the IFT complex B or complex A subunits are described. Most mouse models that are constitutively targeted by genes related to IFT have shown embryonic lethality (55, 57), and as a result, mouse models that are specifically targeted to IFT genes were produced to identify the role of IFT genes in the kidney. In PKD mouse models targeted by the IFT complex B subunit, deletion of the *Ift20* gene in the collecting duct cells of the kidney is well documented. Because *Ift20* belongs to IFT complex B, which has a role in cilia assembly (57), inactivation of *Ift20* gene may cause defects in cilia formation. As expected, polycystic kidney, accompanied by the absence of cilia and centrosome defects such as mislocalization and overduplication leading to misorientation of the mitotic spindle, is observed in the *Ift20* targeted renal collecting duct cells (57). In the PKD mouse model targeted by the IFT complex A subunit, inactivation of the *Ift140* gene in the collecting duct cells of the kidney is well documented. This mouse model exhibits severe polycystic kidneys accompanied by an increase in canonical Wnt signaling (60). However, the renal cilia phenotype for *Ift140*-deleted kidneys is slightly different from those of *Ift20*-deleted kidneys. Renal cilia are almost completely absent in *Ift20*-deleted kidneys, but inactivation of *Ift140* in the kidney results in short or stumpy cilia despite cystic renal epithelial cells in the late stage (60). These studies indicate that defects in IFT complex B commonly induce loss of renal cilia while defects in IFT complex A appear to induce short or truncated renal cilia instead of lack of cilia, suggesting that normal renal cilia structure is critical for repressing the cystogenesis mechanism in PKD.

Another PKD mouse model targeted by mutation in non-IFT genes is the juvenile cystic kidney (*jck*) mouse, which has a missense mutation in the *Nek8* gene encoding

serine/threonine kinase, NIMA (never in mitosis A)-related kinase 8 (68). The NIMA protein is known as the mitosis regulator and controls cell cycle entry (69). It has been suggested that cell cycle regulators may be involved in the regulation of primary cilia structures because primary cilia are absorbed into the cells during the cell cycle, resulting in disassembly of the primary cilia (70). Therefore some regulators related to cell cycle progression, such as the NIMA protein, may have an effect on the primary cilia structure. Consistent with this prediction, lengthened renal cilia are observed in the kidneys of *jck* mice with the accumulation of PC1 and PC2 expression along the cilia (71). With these ciliary defects, the *jck* mouse model shows the PKD phenotype in multiple nephron segments with increased levels of cAMP, resulting in an increase in fluid secretion into the lumen and renal cell proliferation (71).

These PKD mouse models showing defects in renal cilia suggest that ciliary defects, including normal cilia without polycystin, stumpy cilia, and lack of cilia, are a driving force in the development of cystic kidney, and that cilia are important to maintain normal physiology in the kidney. Therefore, understanding the pathological changes that are specifically influenced by renal ciliary defects is important to elucidate the mechanism underlying renal cystogenesis.

Aberrant signaling pathway induced by ciliary defects in PKD

Unlike motility cilia, primary cilia have no motility but are considered cellular antenna that transduce extracellular environmental changes to intracellular signaling molecules (72), suggesting that defects to the cilia lead to aberrant multi-signaling pathways. In PKD with ciliary defects, many signaling pathways related to cell proliferation are disrupted (73). Among the pathways disrupted in PKD, mitogen-activated protein kinase (MAPK) and mammalian target of rapamycin (mTOR) pathways are commonly activated in PKD (74, 75).

The primary cilium in the renal epithelial cell protrudes from the plasma membrane into the lumen to sense flow stimulation through the renal tubules (16). Flow stimulation induces the bending of intact cilia with PC1/PC2 calcium channels (16, 76), which leads to an increase in intracellular calcium levels followed by the release of calcium from the endoplasmic reticulum (ER). Increased levels of intracellular calcium induce suppression of the Ras/Raf/Mek/Erk pathway by regulating cAMP (42, 77). In contrast, perturbation of flow sensing occurred in PKD in the absence of cilia, resulting in the decrease of intracellular calcium levels (78). Decreased intracellular calcium levels induce cAMP activation, leading to activation of the Ras/Raf/Mek/Erk pathway. Hence, increased cell proliferation and fluid secretion into the lumen are observed in many PKD models with cilia defects (79).

The mTOR signaling pathway plays a role in regulating cell size and metabolism (80). Accumulated data suggest that hyper-activation of the mTOR pathway is observed in various PKD mouse models (75, 81). Based on these data, many research groups have tried to find the regulatory mechanism of the mTOR pathway in PKD models with cilia defects. There is a paper elucidating the role of renal cilia in regulation the mTOR pathway (82). This paper suggests that Lkb1 and AMPK proteins, localized at the basal body of normal primary cilia, repress the mTOR signaling pathway under flow conditions to reduce cell size (82). However, enlarged cell size and hyper-activation of mTOR signaling are observed due to a decrease in the responsiveness to flow stimulation in cilia-defective PKD (kidney-specific inactivation of *Kif3a*) models (55, 82), suggesting that proteins localized to the basal body of the cilium and normal ciliary structure are critical to regulate mTOR signaling in PKD.

A new ciliary pathway that promotes renal cyst formation was recently reported (56). According to many papers published so far, the presence of renal cilia seems to act as a suppressor for renal cyst growth, but recent studies have demonstrated that primary cilia devoid of polycystin proteins can activate renal cyst growth (56). To prove this idea, a combination of the cilia-defective PKD mouse model and the polycystin-defective mouse model was produced (56). Surprisingly, loss of renal cilia reduced renal cyst size following defects in polycystin proteins, suggesting a new pathway involving cilia-dependent cyst activating (CDCA) mechanisms inhibited by polycystin (56). However, a CDCA-specific pathway or regulator has not yet been identified, so further studies are needed.

In summary, normal primary cilia with polycystin proteins are critical to suppress rapid renal cyst growth by inhibiting the increase of cell proliferation, leading to the onset of PKD. In this chapter, MAPK, mTOR and CDCA pathways are discussed, but Hedgehog and Wnt pathways are also regulated in primary cilia and disrupted in PKD models. Therefore, identification of the role of cilia in PKD and role of polycystins in cilia are helpful to understand PKD pathogenesis and to identify new therapeutic targets for curing PKD.

Conclusion

The relationship between defects in primary cilia and PKD development has been elucidated, but the exact role of the primary cilia and related proteins in PKD remains to be identified. It was recently suggested that various pathogenic proteins observed in PKD models are localized to primary cilia. Also, it has been reported that proteins associated with primary ciliary assembly or with regulating ciliary function play a role in regulating the cell cycle in non-ciliated cells (83), which suggests that ciliary proteins may be essential

for regulating multiple signaling pathways in a cilia-dependent as well as cilia-independent manner. Therefore, elucidating the role of primary cilia or components related to primary cilia will provide new insights into the pathological mechanisms of ciliopathies involving PKD in addition to non-ciliopathies.

Conflict of interest

The authors declare that they have no conflicts of interest with respect to research, authorship and/or publication of this book chapter.

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