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Review Article

# Cyst growth, polycystins, and primary cilia in autosomal dominant polycystic kidney disease

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## Abstract

The primary cilium of renal epithelia acts as a transducer of extracellular stimuli. Polycystin (PC)1 is the protein encoded by the *PKD1* gene that is responsible for the most common and severe form of autosomal dominant polycystic kidney disease (ADPKD). PC1 forms a complex with PC2 via their respective carboxy-terminal tails. Both proteins are expressed in the primary cilia. Mutations in either gene affect the normal architecture of renal tubules, giving rise to ADPKD. PC1 has been proposed as a receptor that modulates calcium signals via the PC2 channel protein. The effect of PC1 dosage has been described as the rate-limiting modulator of cystic disease. Reduced levels of PC1 or disruption of the balance in PC1/PC2 level can lead to the clinical features of ADPKD, without complete inactivation. Recent data show that ADPKD resulting from inactivation of polycystins can be markedly slowed if structurally intact cilia are also disrupted at the same time. Despite the fact that no single model or mechanism from these has been able to describe exclusively the pathogenesis of cystic kidney disease, these findings suggest the existence of a novel cilia-dependent, cyst-promoting pathway that is normally repressed by polycystin function. The results enable us to rethink our current understanding of genetics and cilia signaling pathways of ADPKD.



## Introduction

It has been reported that abnormalities in the structure or function of primary cilia result in kidney cyst growth in animal models and human genetic diseases collectively known as ciliopathies [1–3]. Polycystin (PC)1 has been hypothesized to form a mechanosensitive cation channel complex with PC2 in the primary cilia [4–6]. Functional defects in this complex caused by mutation of *PKD1* or *PKD2* result in autosomal dominant polycystic kidney disease (ADPKD) [7,8]. Primary cilia are membrane-enclosed hair-like projections from the apical surface of renal epithelial cells, facing into the tubule lumen (Fig. 1). Primary cilia are microtubule-based organelles that are ideally positioned to detect extracellular stimuli and to transduce these signals into the cell to elicit physiological responses [6,9]. Experimental evidence that flow-mediated deflection of the cilia induces an increase in intracellular calcium has fostered the hypothesis that cilia may sense flow in the kidney tubule lumens [10–12]. Intraflagellar transport (IFT) is a general ciliary component transport mechanism required for assembly and steady-state maintenance of cilia [13,14]. IFT plays an additional role in regulating cell-cycle progression independent of its function in cilia formation [1]. Despite these data, there remains some lack of clarity on the relationship between PCs and cilia function. Recent studies have generated novel information regarding the genetic and molecular implications of ADPKD, its pathogenesis, and new potential strategies for targeted treatment. In this commentary, new signaling activity of interconnectedness between primary cilia and PCs, and dosage effects of PC are highlighted.

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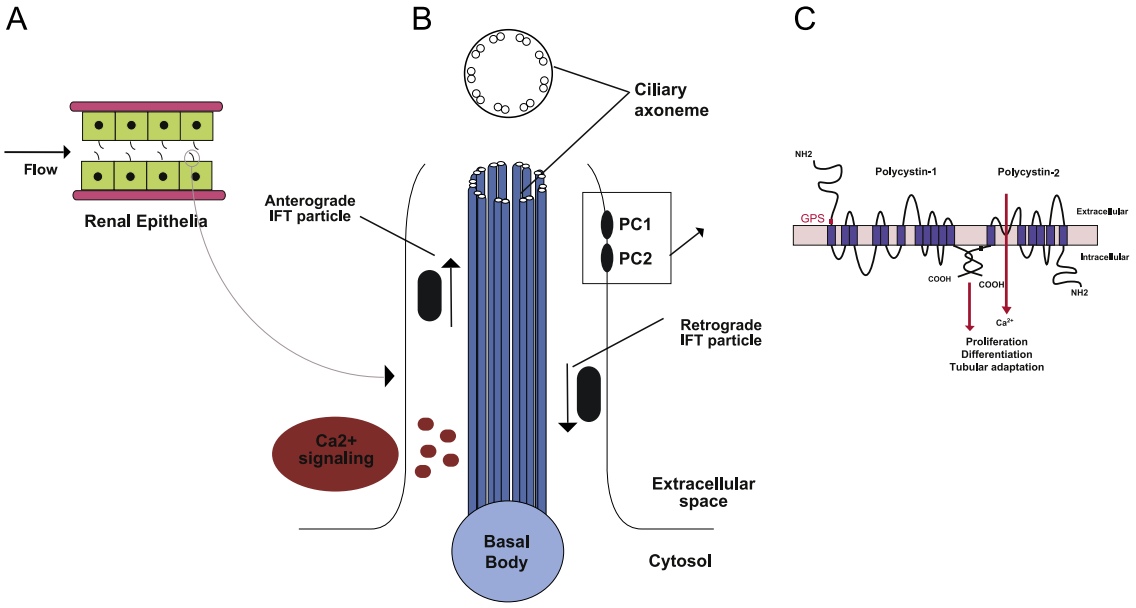


**Figure 1. PCs and cilia.** (A) Renal tubular epithelium depicted as cuboidal cells with apical primary cilia projections subjected to luminal flow. (B) Schematic of 9 + 0 primary cilia. As a microtubule-based structure that imports proteins via anterograde IFT and returns proteins to the cell body via retrograde IFT transport. PC1 and PC2 reside in the cilium membrane and are hypothesized to subsume a local calcium signaling process that may be modulated by mechanical or ligand stimuli. (C) Schematic representations of PC1 and PC2 showing their respective topologies and interaction via coiled coil domains in their carboxy termini. PC1 has the properties of a receptor and undergoes cleavage at the indicated (red letters) GPS sites. GPS site, whereas PC2 is a calcium channel of the TRP family. GPS, G protein coupled receptor proteolytic site; IFT, intraflagellar transport; PC, polycystin; TRP, transient receptor potential. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

## ADPKD

ADPKD is a common, single-gene multi-system disorder. Its prevalence at birth is between 1:400 and 1:1,000 and it affects $>12$ million people worldwide, without regard to sex or ethnicity [5,7,8,15]. The disease is characterized by the development of renal cysts and various extrarenal manifestations. ADPKD results from excessive proliferation of renal tubular epithelial cells and remodeling of surrounding structures, giving rise to growth of epithelial-lined cysts accompanied by fibrosis and accumulation of extracellular matrix. As the disease progresses, this leads to destruction of the normal renal parenchyma, massive renal enlargement, deterioration of renal function, and eventually renal failure in $>50\%$ of affected individuals by late adulthood [5,15]. A two-hit model has been proposed to explain the focal nature of renal cysts and the variability in cyst size in both orthologous mouse models and in humans [16–18]. In this model, a germline and a somatic mutation inactivate the PKD alleles separately. The first hit, a germline mutation inherited from the affected parent, is predisposing but not sufficient for cyst formation. The first hit exists in all cells in the body. The second hit, a somatic mutation in an individual cell, inactivates the normal *PKD1* or *PKD2* allele, and when it occurs in kidney tubule cells, is thought to cause abnormal focal proliferation and tissue remodeling, giving rise to cyst formation [19,20]. Conditional knockout of *Pkd1* in mice indicates that the timing of the somatic second hit mutation affects the severity of cyst progression. Inactivation of *Pkd1* in mice prior to a developmental switch occurring prior to postnatal Day 13 results in severely cystic kidneys within 3 weeks, whereas inactivation at Day 14 and later results in cysts only after 5 months [21]. Multiple genetic mechanisms that result in an imbalance in the expression of either PC1 or PC2 below a critical threshold without complete loss can also cause cyst formation [22,23]. The presence of somatic PKD2 mutations detected in cystic patients with PKD1 germline mutations and increased disease severity in patients with heterozygous germline mutation in both PKD1 and PKD2 offer further support for the two-hit model and the dosage effect hypothesis for cyst formation [24,25].

## ADPKD genes and proteins – *PKD1*, *PKD2*, and PC1 and PC2

*PKD1* mutations account for ~85% of the clinically ascertained disease burden. The *PKD1* gene product, PC1, is a large protein consisting of 4,302 amino acids with a large extracellular amino terminus, 11 transmembrane domains, and a short cytosolic carboxy terminus (Fig. 1C) [5,15]. PC1 is possibly expressed in most nephron segments, despite expression at the tissue level being difficult to determine due to its low protein levels. At the subcellular level, it has been reported that PCs are expressed in several subcellular compartments of renal epithelial cells, remarkably primary cilia, lateral cell to cell junctions, and the endoplasmic reticulum. Investigations in other experiments have demonstrated that the localization of PC fractions to primary cilia is thought to be required for the function of cilia as mechanosensors [2,3,6,20,26].

PKD2, the gene mutated in 15% of polycystic kidney disease cases, encodes PC2 [5,27]. PC2 has been described as a nonselective, calcium-permeable cation channel belonging to the transient receptor potential (TRP) polycystic subfamily of TRP channels [28,29]. PC2 is an integral membrane protein with six transmembrane segments, and both the amino and carboxy termini face the cytoplasmic compartment [30,31]. PC2 contains several trafficking motifs: the RVxP motif at the