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Progress in the understanding of polycystic kidney disease

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Abstract

The function of polycystin proteins and the pathogenesis of autosomal dominant polycystic kidney disease (ADPKD) are not well understood. Studies published in 2018 made important contributions to the understanding of genetic mechanisms, the structure of the polycystin complex and the roles of G-protein signalling and the immune system in ADPKD.

Autosomal dominant polycystic kidney disease (ADPKD) is caused by mutations in *PKD1* or *PKD2,* which encode polycystin 1 (PC1) and polycystin 2 (PC2), respectively. PC1 and PC2 are generally accepted to form and function as a polycystin complex, but the structure of this complex is unclear. Current evidence suggests that germline and possibly somatic mutations to *PKD1* or *PKD2* reduce PC1 or PC2 levels below a critical threshold that is required to prevent cyst formation. The functional effect of mutation may be altered G-protein and cAMP signalling, resulting in disruption of downstream signalling pathways and cystogenesis. The immune system may also play a major part in disease progression in ADPKD. Key studies published in 2018 made important contributions to the understanding of these areas[1-5]

Evidence that cysts can develop when some polycystin is present and that ADPKD severity is associated with the level of functional polycystin has led to questions regarding the universality of the proposed two-hit mechanism by which somatic second hits to the normal allele of *PKD1* or *PKD2* promote cyst initiation. In 2018, whole-exome sequencing (WES) and careful analysis of the duplicated *PKD1* locus were used to investigate the importance of somatic mutations in ADPKD cystic epithelia[1]. This study of 63 kidney cysts from nine patients detected somatic mutations in the disease gene in 90% of cases. In addition, 1,785 possible somatic mutations in 1,477 other genes were detected, showing that cystic epithelia are prone to somatic mutation, although a clear single locus driving cystogenesis (beyond the ADPKD genes) was not identified. Notably, *PKD1* somatic mutations were identified by WES in only 43% of *PKD1* cysts, providing further evidence that an unoptimized capture approach is not ideal for screening this locus[6]. This important study strengthens the argument that loss of polycystin function has a key role in cystogenesis and brings cyst analysis into the genomic era. However, as only large cysts (1.5–20.0 cm) were analysed and variant allele counts were not provided, questions remain as to whether somatic mutations

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Competing interests

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cause initiation of cyst development or provide a growth or survival advantage to a formed cyst.

Cryogenic electron microscopy (cryo-EM) methodologies generate high-resolution structures of large membrane proteins — an important step towards understanding function. In 2016, cryo-EM defined the structure of the homotetrameric PC2 channel[7]. In 2018, the structure of a PC2 plus PC1 complex with a 3:1 ratio and overall dimensions of 130 Å×110 Å×130 Å was resolved to 3.6 Å (REF.[2]) (FIG. 1. The voltage-gated ion channel (VGIC) fold consisting of the last six transmembrane domains of PC1 and a regulating TOP domain (homologous to that of PC2) substitutes for one PC2 molecule in the complex. The other five transmembrane domains and the PLAT (polycystin 1, lipoxygenase and α-toxin) region of PC1 constitute the amino-terminal domain that associates with the 24 transmembrane domains of the four VGIC regions. The structure of the last transmembrane domain of PC1 is distinct from the corresponding domain of PC2 in that it splits into two segments offset at 120° and lacks a PC2 selective filter and supporting pore helices. This region contains three positively charged residues facing the pore that would likely impede Ca^{2+} permeability. A caveat of this study is that the extracellular region of PC1 (to amino acid 3,048) and the cytoplasmic tails of PC1 and PC2 were removed to enable purification of the complex, and the location of the complex is unknown. Nonetheless, this high-resolution structure helps to interpret detected variants, provides a basis for better understanding of polycystin function and suggests that the PC1–PC2 complex does not function as a Ca^{2+} channel.

PC1 is a large transmembrane protein with many similarities to the adhesion G-protein coupled receptor (GPCR) family, including a large extracellular region with adhesion domains, a GPCR autoproteolysis site within a larger GPCR autoproteolysis-inducing domain and an intracellular carboxyl terminus harbouring a G-protein binding domain (GBD). In 2018, a study using the *Xenopus* pronephric kidney showed that a carboxy-terminal tail construct containing the GBD of PC1, but not a construct that lacked this domain, rescued a *pkd1* morphant; the C-terminal tail of PC1 binds the G-protein α subunits Gnas, Gnai1, Gnai2 and Gna14 with high affinity; and knockdowns of select G-protein α subunit combinations display a *Pkd1* morphant phenotype that is reversed by inhibiting downstream G-protein β/γ signalling but not by activating Gnas, Gnai or Gna14 downstream signalling[3]. These observations were confirmed in murine *Pkd1*-null 3D cultures. The researchers propose that G-protein α subunits bind to the GBD of PC1 and sequester free β/γ subunits, preventing them from interacting with α subunits bound to GPCRs. By contrast, loss of PC1 increases the pool of free β/γ subunits and results in GPCR hyper-reactivity, which may contribute to the increased disease severity that is associated with *PKD1* compared to *PKD2* mutations and to the effectiveness of therapies targeting GPCRs in ADPKD. These findings also suggest possible additive effects of therapies targeting both G-protein α (for example, vasopressin V2 receptor antagonists) and β/γ (for example, gallein) signalling. A recent report that PC1 with a single amino acid deletion in the GBD cannot activate heterotrimeric G-protein signalling and support the channel activity of PC2 is not entirely consistent with the proposed model but supports the functional importance of this PC1 domain[8].

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Innate and adaptive immunity have both been implicated in ADPKD pathogenesis. Monocyte chemoattractant protein 1 (MCP1; also known as CCL2) recruits monocytes into sites of inflammation and controls T helper lymphocyte differentiation towards type 1 (T_H1) or T_H2 phenotypes. MCP1 accumulates in cystic kidneys, and alternatively activated macrophages promote cyst growth. Moreover, urine MCP1 excretion is associated with kidney function decline, and treatment with tolvaptan lowers urine MCP1 levels[9,10]. Two studies published in the past year strongly suggest that MCP1 has a pathogenic role in ADPKD[4,5].

Viau et al. showed that deletion of *Lkb1*, *Pkd1* or one of three genes that are mutated in nephronophthisis (*Anks3*, *Nek7* or *Nphp1*) in mouse renal tubules promotes MCP1 expression, peritubular accumulation of macrophages expressing the MCP1 receptor (CCR2) and a phenotype resembling nephronophthisis or ADPKD[4]. Simultaneous inactivation of *Mcp1* and *Pkd1* or simultaneous disruption of ciliogenesis (by targeting *Kif3a*) and inactivation of *Pkd1* attenuated macrophage accumulation and the cystic phenotype. The researchers propose that cilia actively promote chemokine signalling and inflammation unless this pathway is suppressed by a module involving LKB1, PC1 and nephronophthisis-associated proteins.

Cassini et al. used mice with inducible kidney-tubule-specific knockout of *Pkd1* alone or of both *Mcp1* and *Pkd1* to investigate the role of MCP1 in ADPKD[5]. In the *Pkd1* knockout, MCP1 upregulation preceded macrophage infiltration. Within 2 weeks after induction, pro-inflammatory macrophages accumulated around nascent cysts and induced tubular cell injury with morphologic flattening and proliferation-independent cystic dilation. At 2–6 weeks these macrophages switched to an alternative activation phenotype and promoted marked cell proliferation and cystic dilatation. In double-knockout mice, MCP1 expression, macrophage numbers, initial tubular cell injury and cyst growth were markedly attenuated. Treatment of *Pkd1*-knockout mice with a CCR2 antagonist starting 2 weeks after induction was also protective. These studies provide a strong rationale for clinical trials of CCR2 antagonists in ADPKD and suggest that the success of such a strategy may require early and prolonged administration.

ADPKD remains one of the most active areas of research in nephrology. The articles reviewed here illustrate the multifaceted character of this research with a shared goal of finding increasingly effective treatments for this disease.

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Key advances

- The identification of high levels of somatic mutations in *PKD1* and *PKD2* in autosomal dominant polycystic kidney disease (ADPKD) cysts demonstrates an important role of polycystin loss in cyst progression[1].
- A high-resolution cryogenic electron microscopy structure of the polycystin 1–polycystin 2 (PC1–PC2) complex provides insights into polycystin function and suggests that this complex does not form a functional Ca^{2+} permeable channel[2].
- PC1 acts as a G-protein coupled receptor (GPCR) that binds Å subunits; loss of the G-protein binding domain of PC1 causes GPCR hyper-reactivity, suggesting possible treatment options for ADPKD[3].
- Cilia actively promote chemokine signalling and inflammation via a pathway that promotes monocyte chemoattractant protein 1 (MCP1) expression; this pathway can be suppressed by a module involving LKB1, PC1 and nephronophthisis-associated proteins[4].
- Expression of MCP1 promotes macrophage accumulation and cystic dilatation; blocking the MCP1 receptor might be an advantageous strategy for the treatment of ADPKD[5].

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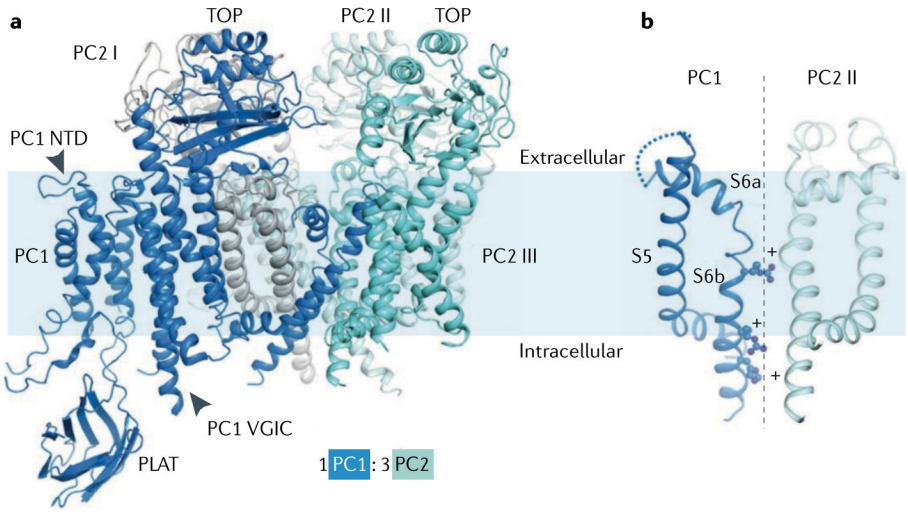

Fig. 1|. The structure of a PC1-PC2 complex.

a | A polycystin complex composed of three polycystin 2 (PC2) and one polycystin 1 (PC1) subunits. **b** | The last transmembrane domain of PC1 (S6) has two offset segments (S6a and S6b) and positively charged residues in the pore (+) that may block Ca^{2+} permeability. NTD, amino-terminal domain; PLAT, polycystin 1, lipoxygenase, and α-toxin region; TOP, TOP domain; VGIC, voltage-gated ion channel. Reproduced with permission from REF.[2], AAAS.