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Present Status and Advances in Autosomal Dominant Polycystic Kidney Disease

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Abstract

Autosomal dominant polycystic kidney disease (ADPKD) is the most common genetic disorder of the kidney. The mainly clinical manifestation is progressive cyst formation in bilateral kidneys, impairs normal renal parenchyma, and ultimately results in end-stage renal disease (ESRD). Extra-renal lesions include cystic liver or pancreas, brain aneurysm and cardiovascular defects. Mutations in either *PKD1* or *PKD2* genes result in the disease, but the former develops more severe clinical phenotypes than the latter. Currently, ADPKD still challenge vast clinicians on account of lacking effective and less side-effect therapy. Intensive study of molecular mechanism of the disease can establish theoretical basis for potential therapeutic targets and guide clinicians to develop new approaches in treatment of this disease. This review will focus on current advances of ADPKD pathogenesis which may benefit the translational therapy and precision medicine for the disease treatment.

Keywords: ADPKD; Cystogenesis; *PKD1*; *PKD2*; Cell signaling

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Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is the most common monogenic disorder which is characterized by progressive fluid-filled cysts in the kidney. It occurs worldwide and in all races with significant different prevalence in different region: United States (1/400) [1], Denmark (1/1000) [2], Walsh (1/2459) [3], Japan (1/4033) [4]. Most recent statistics indicated that the prevalence of ADPKD in Europe is estimated to be 1/2500 [5]. ADPKD is the fourth most common single cause of end-stage renal failure (ESRD), which occurs in 50% of affected individuals by the age of 60 years [6]. The high risk factors that affects the progression ESRD include *PKD1* mutation [7], bigger Total Kidney Volume (TKV) [8], younger diagnosed age, early onset of hypertension [9], proteinuria and microalbuminuria [10,11].

ADPKD is a systemic disease with various extrarenal manifestations including hypertension [12,13], liver and pancreatic cysts [14], intracranial aneurysms [15], aortic root and thoracic aorta abnormalities [16-18], mitral valve prolapse [19,20] and abdominal wall hernias [21,22]. 50% to 70% of patients with ADPKD display hypertension, mostly occurring before they develop a significant decrease in renal function [23,24]. Up to 83% of ADPKD patients have hepatic cysts. However, there is no overt clinical symptoms and rarely cause liver failure [25,26]. The prevalence of intracranial aneurysms (ICA) among ADPKD patients is about 12% [27]. A family history of intracranial hemorrhage can significantly increase the risk of ICA [28]. Therefore, examination and evaluation of extrarenal organ of ADPKD patients is also very important.

At present, there is no safe and effective treatment of ADPKD in clinic. Therefore, understanding the pathogenesis of ADPKD may provide a new therapeutic target for the clinical treatment and lay the foundation for the development of various biological and drug treatments for ADPKD.

PKD Genes and Proteins

ADPKD is genetically heterogeneous with two genes identified, *PKD1* [ch16p13.3, 46 exons] and *PKD2* [ch4q21, 15 exons], which encode the proteins polycystin-1 [PC1] and polycystin-2 [PC2], respectively. Amongst ADPKD patients, 85-90% of cases result from mutations in *PKD1*, while another 10-15% of cases are caused by mutations in *PKD2* [29]. Polycystin-1 is a transmembrane mechano/chemo-sensor receptor and polycystin-2 is a non-selective cationic channel belongs to the subfamily of transient receptor potential (TRP) channels. Polycystin-1 contains 4302 amino acids and consists of a huge extracellular domain, 11 transmembrane domains and a shorter cytoplasmic tail domain

[30,31]. Polycystin-1 is found in most segments of the nephron and is distributed in a variety of subcellular structures such as the primary cilia, cytoplasmic vesicles, plasma membrane at focal adhesions, desmosomes, adherens junctions, and possibly endoplasmic reticulum and nuclei. Among them, polycystin-1 distributed in primary cilia is considered to play an important role in the mechano/chemo-sensor function [32-34], whereas polycystin-1 distributed in the side wall and the basal body participates in the formation of intercellular adhesion and focal adhesion [35]. In addition, a cleavage product of polycystin-1 that includes the C-terminal tail can translocate to the nucleus and regulate gene transcription [36,37].

Polycystin-2 (968 amino acids) contains a short N-terminal cytoplasmic region with a ciliary targeting motif, 6 transmembrane domains, and a short C-terminal portion [38,39]. Polycystin-1 physically interacts with polycystin-2 through a coiled-coil domain in the C-terminal portion which forms the polycystin-signaling complex that play a role in chemosensory or mechanosensory signal transduction [40]. Disruption of both gene products results in similar clinical phenotypes. Polycystin-2 is distributed in all nephrons except glomeruli which subcellular localized in the endoplasmic reticulum and cilia [41]. Polycystin-2 is a non-selective cation channel belonging to the transient receptor potential cation channel family [42]. It regulates intracellular Ca^{2+} levels and affects various cellular activities such as cell proliferation and differentiation and epithelial cell polarity [43-45].

ADPKD and Cilia

Primary cilia are microtubule-based antenna-like organelles protruding from the surface of vertebrate cells that mediate a number of signaling pathways during development and tissue homeostasis [32]. Defects in primary cilia are thought to play an important role in polycystic kidney disease [46,47]. According to the current hypothesis, primary cilium is a kind of sensory organelle. Polycystin-1 and polycystin-2 co-localized in primary cilia forming PC complex through the C-terminal cytoplasmic tail domain [40]. PC1 exert the role of mechano/chemo-sensor, response to mechanical or fluid-induced cilia bending, and modulates Ca^{2+} channel activity of polycystin-2, causing changes in intracellular Ca^{2+} levels [48]. Growth and maintenance of primary cilia relies on the Intraflagellar Transport (IFT) system [49,50], which transports various proteins to and from cilia, including polycystin-1 and polycystin-2, via kinesin and dynein [51-53]. Thus, besides the absence of polycystins that leads to polycystic kidney disease phenotype, IFT system deletions such as deactivating the IFT system components Kif3a, Ift20 and Ift88 in mouse models also cause polycystic kidney disease phenotype [54]. Although cilia loss is associated with cystic kidney disease, recent studies have shown that there is no evidence of primary cilia-associated Ca^{2+} influx in both the renal tubules and cell lines stimulated by fluid flow at physiological levels [55]. Therefore, the role and function of fibril in ADPKD remains to be further studied and elucidated.

Discussion

Signaling pathways as targets in PKD treatment

Many signaling pathways control ADPKD cyst formation such as the mammalian target of rapamycin (mTOR) [56,57], cyclic adenosine monophosphate (cAMP) [58,59], Wnt signaling pathway [44, 60], G protein coupled receptor [GPCR] [61] and Signal Transducer and Activator of Transcription (STAT) signaling pathway [62] **(Figure 1).**

mTOR pathway

The serine/threonine kinase mammalian target of rapamycin (mTOR) is an evolutionary conserved signaling molecule, integrating a broad spectrum of signals and environmental cues, including oxidative stress, availability of nutrients and energy. Under physiological conditions, growth and proliferation requires both an appropriate stimulus and a favorable environment [63]. In contrast, malignant (cancer) and benign human proliferative disorders including ADPKD are frequently accompanied by aberrant activation of the mTOR signaling pathway [57,64,65]. In ADPKD, deletion of polycystin-1 in tubular epithelial cells results in decreased expression of the TSC1/TSC2 complex, which in turn reduces mTOR inhibition, resulting in over activation of mTOR and subsequent abnormal proliferation of epithelial cells [66]. Results from animal experiments also show that mTOR inhibitors are able to slow the increase of kidney volume in ADPKD models of ADPKD [67].

cAMP pathway

As a second messenger, cyclic adenosine monophosphate (cAMP) involved in cell proliferation, differentiation, DNA synthesis and is capable of regulating a number of cellular biological processes, including electrolyte and humoral transport. The level of cAMP is determined by the activity of adenylyl cyclase (AC) and phosphodiesterase (PDE), both of which mediate the synthesis and degradation of cAMP and are regulated by Ca^{2+}. Elevated intracellular cAMP levels were observed in PKD patients and in various animal models of PKD [58,68]. Increased levels of cAMP in ADPKD renal epithelial cells activates the B-Raf/MEK/ERK signaling pathway [69,70] and promotes cell proliferation. Accordingly, treatment of vasopressin V2 receptor antagonist (Tolvaptan) which reduce cAMP level in ADPKD animal models and patients exhibits slowed renal volume increase and improved renal function [71,72]. However, but the resulting damage to liver function and other toxicities (such as polyuria) severely limit the wide range of clinical applications of this drug.

Wnt pathway

Wnt signaling pathway play pivotal role in cell proliferation, migration, apoptosis and organ development, including the kidneys. There are two main types of Wnt signaling pathways: canonical Wnt signaling and non-canonical Wnt signaling. Recent studies have demonstrated that human cystic disease may involve Wnt signal transduction [60,73]. Transgenic mouse for β-catenin

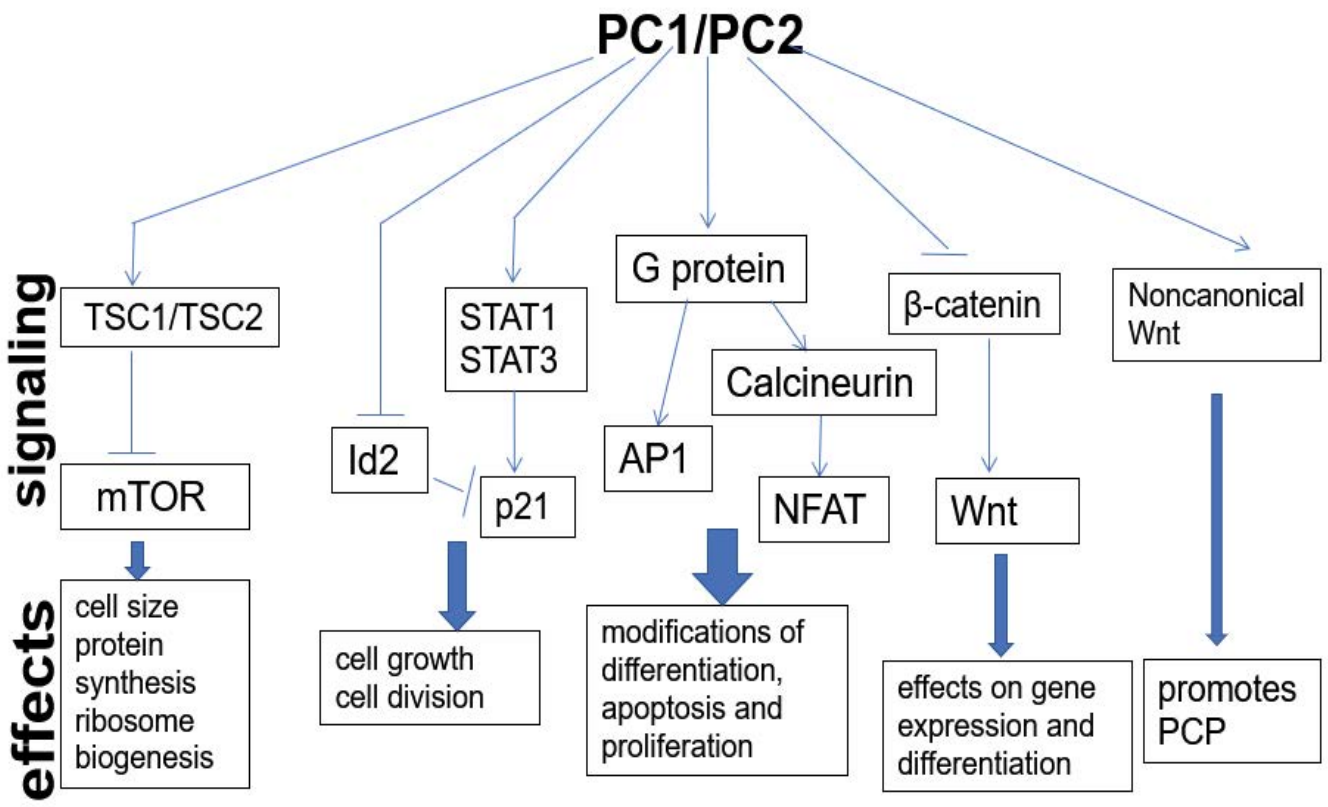

Figure 1 Signaling pathways involved in ADPKD.

exhibits severe PKD phenotypes, showing that the upregulation of β-catenin alone is sufficient to induce cyst formation in the kidney [74]. Other reports demonstrated that PC1 CTT co-localizes with and binds to b-catenin in the nucleus. The PC1 CTT inhibits the ability of both b-catenin and Wnt ligands to activate TCF-dependent gene transcription, which is a major effector of the canonical Wnt signaling pathway [75]. Our work also found that loss of PC2 can increase the expression of b-catenin, axin2 and c-Myc. This suggests that PC2 may play a function role in inhibition of β-catenin-dependent Wnt signaling [44]. All of these results indicated that have shown that the loss of *Pkd1* and *Pkd2* account for abnormal activation of Wnt signaling pathways and cystogenesis.

G protein signaling pathway

Although there is a difference between the structure of PC1 protein and the classical G protein-coupled receptor (GPCR), the GPS site near the extracellular domain of polycystin-1 play similar biological function of GPCR. Disruption this site result in the formation of renal cysts in mice [76]. Polycystin-1 also directly binds to the G protein subunit and activates downstream molecules such as c-Jun N-terminal kinase, AP-1 transcription factor, and activated T cell signaling cascade nuclear factor which regulate normal cell proliferation differentiation and apoptosis [77,78]. In ADPKD, polycystin complex inhibits PC1-mediated G protein signaling pathway activation. Loss of polycystins give rise to activation of G protein signaling pathway thereby promotes cyst formation [79]. In addition, G-protein-signaling modulator 1 (GPSM1) is able to upregulate the channel function of the polycystin complex via the G protein subunit. In the *Pkd1* mouse model, complete deletion of GPSM1 promotes cyst formation and reduces renal function [80], indicating that GPSM1 may also play a role in GPCR activation of ADPKD.

Signal Transducer and Activator of Transcription (STATs)

JAK/STAT signal pathway is a cytokine-stimulated signal transduction pathway involved in many important biological processes such as cell proliferation, differentiation, apoptosis and immune regulation. Studies have shown that polycystin-1 participate in the regulation of JAK/STAT signaling pathway. PC1 activates STAT3 more under the mediation of JAK2 and thus regulates DNA transcriptional activity of epithelial cells [37]. STAT3 is significantly activated in cyst-lining epithelial cells of human ADPKD patients and mouse model as well as in the developing and postnatal kidneys, but inactivated in mature kidneys. These results demonstrated that the STAT3 signaling pathway is regulated by PC1 and serve as a driver of renal epithelial proliferation during normal kidney development and renal cyst growth. Studies have shown that inhibition of STAT6 by leflunomide (LEF) slows cyst growth in ADPKD mouse models [81].

Conclusion and Future Perspectives

Currently, abnormal proliferation, loss of polarity of epithelial cells and abnormal secretion of fluid are the three key components of ADPKD cyst formation [82]. The activation of mTOR, GPCR and

Wnt pathways promote the abnormal proliferation of epithelial cells. The activation of cAMP/CFTR pathway increases the fluid secretion in the cyst. In-depth study of these mechanisms is expected to help people find potential targets for the treatment of ADPKD. At present, there are some clinical trials targeting different molecules of these pathways. However, either poor efficacy or intolerant side effects limit widespread use in clinic. Therefore, the discovery of new therapeutic targets and new drugs based on various molecules and signaling pathways will have great practical significance in the clinical treatment of ADPKD.

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