

Ciliotherapy – New Opportunity for Targeted Therapy in Autosomal Dominant Polycystic Kidney Disease

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Abstract

Autosomal dominant polycystic kidney disease (ADPKD) is a genetic disease which affects nearly 12 million people in the world. Despite the intensive development of new treatment options, hemodialysis and renal replacement therapy remain the only effective treatment of the end-stage disease. However, recently there has been a significant progress in understanding the molecular pathogenesis of the disease, including the discovery of the role of the primary cilium. Recent studies have unequivocally confirmed that the change in the length of the primary cilium is an important trigger of pathological processes that results in the development and progression of ADPKD. The resumption of the primary cilium length by pharmacological regulation can stop cystic growth, prevent fibrosis, and improve kidney function. These results have opened a new era in the development of targeted drugs, so-called ciliotherapy. Early pre-clinical testing of new potential agents has brought promising results. However, there are many challenges in drug development and design of clinical trials in ADPKD, which must be overcome. This review summarizes the state of knowledge about the key aspects of the primary cilium in pathogenesis of ADPKD and introduces the latest information on novel compounds that have a great potential in suppressing the development and progression of the disease.

Keywords: Primary cilium; Cystogenesis; Fibrogenesis; Targeted therapy

Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is the most common type of renal ciliopathies. It globally affects more than 12 million people, regardless of gender and ethnicity. The progression of the disease leads to the destruction of the renal parenchyma, massive enlargement of the kidney, deterioration of its function, and finally to the end-stage renal disease (ESRD), which affects more than 50% of patients. Dialysis and kidney transplantation are the only treatment option for patients with ESRD [1]. The basis for the development of effective treatments that could prevent the development of the disease or slow its progression is to reveal the exact mechanism of the pathogenesis of the disease at the molecular level. In recent years, there has been a significant progress in this area that triggered intensive development of targeted therapy.

It has been known for several decades that ADPKD is a genetically heterogeneous disease caused by germline mutations in the *PKD1* (polycystic kidney disease 1) and *PKD2* (polycystic kidney disease 2) genes encoding the polycystins [2]. For a long time, the model of cystogenesis in ADPKD was based on the “two-hit” theory, analogous to the Knudson hypothesis of cancer development. According to this model, the formation of cysts is caused by the loss of function of both alleles of the *PKD1* or *PKD2* gene, following the somatic mutation of the second allele [3]. However, investigations of the pathogenesis of ADPKD at the molecular level have confirmed that the loss of the two alleles is not sufficient for the formation of cysts. It follows then that there must be another mechanism underlying this process [4].

Further research studies of these mechanisms have focused on the analysis of signaling pathways. Results of first studies confirmed that renal cysts are characterized by an abnormal proliferation of cells resembling a benign form of neoplasia with the increased activity of mTOR (mammalian target of rapamycin), cAMP (cyclic adenosine monophosphate) and EGFR (epidermal growth factor receptor) signaling pathways [5,6]. Pharmacological research has been focused on

monitoring the effectiveness of targeted drugs that inhibit the activity of these proliferation signals. However, their effectiveness in ADPKD was not sufficient. Despite their preventing the increase in total kidney volume, they were not able to improve kidney function effectively. In addition, studies of the molecular pathogenesis of ADPKD confirmed that renal cysts are not derived from the active proliferation of cells. The activation of these signaling pathways is probably not initiating the event of cystogenesis, which may explain the ineffectiveness of targeted therapies [7].

Recent studies have revealed that the mechanism of activation of the cystic growth and the rate of progression are directly regulated by the primary cilium and are independent of the activity of known signaling pathways [8]. The length of the primary cilium is a direct indicator of its proper structure and functions. The cells of nephrons and collecting ducts have a length of the primary cilium in the range of 1–3 μm under physiological conditions [9]. However, the epithelial cells of renal cysts show an absence or a shortening of the primary cilium. On the contrary, the first stages of interstitial fibrosis are associated with the extension of primary cilia [10]. Many studies have found that the change in the length of the primary cilium is an important trigger of various pathological processes in ADPKD [11,12]. Results of first pre-clinical studies have confirmed that pharmacological normalization of ciliary length can achieve the arrest of cystic growth, restoration of

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renal function, and prevention of the development of kidney fibrosis. The restoration of ciliogenesis thus represents a new strategy for the development of treatment in ADPKD and other ciliopathies.

The role of the primary cilium in cystogenesis

Primary cilia are structurally homogenous organelles that project from the surface of the plasma membranes of almost all the cells of the body. This unique localization allows them to respond to extracellular stimuli and their transmission to the nucleus [13]. Extensive research studies have confirmed that the primary cilium plays a key role in cystogenesis. These studies arrived at the following conclusions:

- Protein products of genes whose mutations are associated with the development of renal cystic disease are localized in the primary cilium [14].
- The main features of renal cyst epithelial cells are functional and structural abnormalities of the primary cilium. Most often it is a lack or shortening of the primary cilium and the presence of typical cystic pattern associated with deregulated proliferation and apoptosis [15].
- Polycystins and ciliary proteins control the transmission of signaling pathways, which show a disturbance of activation in the epithelial cells of the cystic kidney [16].
- The primary cilium plays an important role in the direction of fluid flow into the tubular lumen, which is effected by bending its outer structure. Renal epithelial cells respond to the bending by increased levels of intracellular Ca^{2+} . The absence or shortening of the cilium results in an increased fluid flow, reduced levels of Ca^{2+} and subsequently increased levels of intracellular cAMP [17].
- The restoration of the structure or function of the primary cilium can arrest the formation of renal cysts and slow the progression of the disease [8].

The role of the primary cilium in the induction of renal fibrosis

The expansion of renal cysts is associated with progressive fibrosis, which has a significant impact on the reduction of renal function and gradually leads to ESRD. The process of tubular interstitial fibrosis comes as a consequence of an excessive deposition of extracellular matrix into the interstitium of the kidney, which is caused by activated forms of fibroblast called myofibroblasts. Recent studies have confirmed that the primary cilium is involved in the formation of myofibroblasts. Myofibroblasts arise from mesenchymal or epithelial precursor cells through epithelial-myofibroblast transition (EMyT) [18]. The initial phase of EMyT is characterized by a significant extension of the primary cilium, likely due to the loss of adherens junctions. This extension results in an increased production of glioblastoma-associated oncogene homolog protein (GLI), which is an essential component of the signaling pathway of the primary cilium known as Sonic-Hedgehog (Hh pathway). Consequently, myofibroblasts are formed, accompanied by a loss of the primary cilium regardless of the type of precursor cell [19]. The restoration of the primary cilium length may be an appropriate therapeutic target leading to the prevention of progression of ADPKD.

Specific inhibitors that restore the length of the primary cilium

Considering the growing evidence which has shown the role of the

primary cilium in the cystogenesis and progression of ADPKD, there is an increasing need to identify pharmacological possibilities of its modulations. Currently, compounds have been found that restore the length of the primary cilium and consequently prevent the formation of cysts, development of fibrosis and complications associated with ADPKD.

Inhibitors of histone deacetylases

There has been accumulating evidence that identifies histone deacetylase 6 (HDAC6) as a major driver of ciliary disassembly, suggesting that its inhibition may lead to the increase of the cilium length. HDAC6 causes a shortening of primary cilia through several different mechanisms. It is a cytoplasmatic enzyme that mediates deacetylation of α -tubulin and cortactin, important components of cilia which contribute to microtubule destabilization and ciliary disassembly. Cortactin interacts with filamentous actin (F-actin) after deacetylation and promotes polymerization of the actin, leading to ciliary resorption [20].

The small-molecule compounds that inhibit the deacetylase activity of HDAC6 have been demonstrated to be capable of restoring ciliary structure and function in several different ciliopathies. Tubacin, the first reported HDAC6 selective inhibitor, blocks the deacetylation of α -tubulin in mammalian cells and protects cells from HDAC6-induced ciliary disassembly without affecting histone acetylation, gene expression, or cell progression. A recent study confirmed that a pharmacological inhibition of HDAC6 led to the attenuation of the progression of renal fibrogenesis and reduction of cyst formation in polycystic kidney disease [21]. Similarly, it has been found that the inhibition of HDAC6 through tubacin leads to the decrease in differentiation of the adipocyte and may also prevent the development of obesity associated with Bardet-Biedl syndrome. Gene products in the pathogenesis of nephronophthisis also interfere with the disassembly of the primary cilium. Because the inhibition of HDAC6 increases the length of the primary cilium, this approach may also be beneficial in patients with nephronophthisis [22].

Inhibition of cyclin-dependent kinase 5 (CDK5)

CDK5 is a multifunctional kinase that plays an important role in regulating diverse cellular functions, including the regulation of the primary cilium length. CDK5 regulates the length of the primary cilium by affecting the dynamics of tubulin through its substrate, known as collapsin response mediator protein 2 (CRMP2) [23]. The function of CDK5 in polycystic kidney disease was established in mouse mutant juvenile cystic kidney (JCK) with a conditionally inactivated CDK5 gene. The primary cilia of kidney epithelial cells were lengthened in JCK mice in comparison to wild-type controls. The knock-down of CDK5 resulted in a significant shortening of the cilium length. The impact of pharmacological inhibition of CDK5 on the restoration of cellular differentiation was evaluated using the specific inhibitor R-roscovitine. This inhibitor markedly reduced the cilium length to levels comparable to controls, while it did not abrogate cilia formation. The loss of CDK5 led to the shortening of cilia length and consequently to the reduction of cystogenesis, improved kidney function, and normalization of morphology in cystic renal epithelial cells [24]. CDK5 is therefore a new attractive therapeutic target for the treatment of polycystic kidney diseases.

Inhibitors of GLI proteins

As mentioned above, an overexpression of GLI proteins is a characteristic feature of myofibroblasts and their precursors. Current

research is focused on a direct inhibition of GLI overexpression. Darinaparsin, an organic arsenical compound, directly targets the GLI2 protein and induces an arrest of cell cycle in kidney myofibroblast, thereby preventing the proliferation of myofibroblast and ameliorating kidney fibrosis *in vivo*. Besides Darinaparsin, GANT61, a small-molecule inhibitor of GLI, also displays the ability to ameliorate kidney fibrosis in mice, even when it is administered after kidney injury [25]. However, it is important to consider how these drugs will behave in the context of primary cilia in the human kidney. Understanding the relationships between clinical inhibitors of the Hh pathway and the presence or absence of primary cilia may be critical for the effectiveness of these drugs. Further work is needed in this area to identify molecular mechanisms of these interactions.

Inhibition of reactive oxygen species (ROS)

Recent data demonstrated that the excessive production of reactive oxygen species (ROS) during ischemia-reperfusion injury (I/R) caused variability in the primary cilium length [26]. The role of ROS in altering the length of the primary cilium has been intensively studied with the use of Mn (III) tetrakis (1-methyl-4-pyridyl) porphyrin (MnTMPyP). MnTMPyP is an antioxidant which reduces the formation of superoxids. The result of this treatment was obtained in a study that confirmed the elongation of the primary cilium in the remaining kidney, following a unilateral nephrectomy in response to increased ROS [27]. After the nephrectomy, the increased ROS occurs as a result of the reduction of renal mass, which leads to the rise of glomerular flow and hypertrophy of the tubular epithelial cells in the remaining kidney. The increase of ROS directly correlated with the elongation of the primary cilium. The primary cilium elongation in the remaining kidney was associated with cell cycle and cell differentiation. MnTMPyP treatment rapidly normalized of the primary cilium length concomitant with a decrease of oxidative stress and a morphological recovery of the kidney. These data demonstrate that the regulation of the primary cilia length may be necessary for the compensation and maintenance of renal function following a reduction in total renal mass.

The positive impact of antioxidant treatment in ADPKD has also been confirmed in a recent study investigating the therapeutic efficacy of Resveratrol [28]. The effect of Resveratrol was studied in *in vivo* and *in vitro* experiments on mouse models of ADPKD at 200 mg/kg per day for five weeks. Treatment with this inhibitor significantly reduced macrophage infiltration in renal tissue, the total number of cysts, and the proliferation index. Furthermore, statistical improvement was confirmed in the concentration of creatinine and urea in the blood, indicating a reformation in renal function. However, other studies have found that Resveratrol activates the signaling pathway of SIRT (sirtuin), which, on the other hand, can stimulate the progression of the disease [29]. Future studies investigating the efficacy of this inhibitor will therefore need to focus on identifying inter-relationships of these signaling pathways, defining the maximum dose of the drug and determining the safety of this treatment.

Obstacles to the development of targeted therapy in ADPKD

Whether or not “ciliotherapy” will be successful in clinical trials remains to be determined by subsequent studies. However, it will first need to overcome a number of obstacles related to the design of clinical trials, which have been hindering the development of new drugs in ADPKD so far.

The first obstacle to the development of targeted therapy is the fact that the majority of ADPKD patients do not require native

nephrectomy and cystic kidneys are not generally biopsied for technical and ethical reason. Consequently, the most commonly used materials for pre-clinical testing are exist cell lines and the rodent model of ADPKD. These models however do not completely mimic the human disease [30]. In humans, ADPKD is a genetically heterozygous, slowly progressive disease, whose course is characterized by the occurrence of cysts emerging over several decades of the patient's life. By contrast, the rodent models of ADPKD require a homozygous deletion of the gene immediately after birth or in early embryonic life, which leads to an accelerated progression of the disease with numerous cysts developing simultaneously [31]. Recent developments of hypomorphic or delay-onset disease model will hopefully help overcome this difficulty [32,33]. The second obstacle posed by the use of animal models is the difference in the structure and size of the kidney. Rodent kidney is smaller and simpler in structure than human kidney, so consequences of the expansion of cysts may not reflect the actual state of damage [34]. The solution may be the use of human-induced pluripotent stem cells (iPSCs), which offer a new model system for the investigation of the pathophysiology of the disease [35].

Another problem in the transition of pre-clinical studies into successful clinical trials for ADPKD is the lack of early clinical biomarkers for evaluating biological effectiveness. Therefore, current research in this field will need to concentrate on the identification of sensitive biomarkers which will be able to predict the biological activity of ciliotherapy.

Likewise, a number of inhibitors which have demonstrated effective restoration of the cilium length belong to the group of anticancer drugs. The utilization in ADPKD of these drugs, which are most often the subject of research, is questionable. A reason is need for a long-term treatment for ADPKD patients, which will begin at a young age, or even in the asymptomatic stage of the disease. However, anticancer drugs are toxic with prolonged treatment and therefore are administered for a short duration of time, lasting only until the disappearance of the original disease [36]. Further studies will be carried out to determine the optimal dosage of the drugs to ensure their tolerability and maximum safety.

The next challenge lies in recognizing all the factors which mutually cooperate on the regulation of ciliary length and can contribute to the development of acquired or primary resistance. A precise detection of the genome heterogeneity of ADPKD and the emergence of driver mutation which can equally affect the length of the cilium will be the basis for a successful development of targeted therapy.

Conclusion

Recent advances in understanding the role of primary cilia in the pathogenesis of ADPKD have opened the door for new era in targeted therapy focused on normalization of ciliary length. Intensive pre-clinical studies in this field have revealed new compounds that effectively prevent the formation of cysts and slow progression of the disease. However, the translation of pre-clinical studies into successful clinical trials requires overcoming many obstacles. In the coming years, intensive studies will continue to tackle these challenges with the aim to help accelerate the progress of clinical trials. The resolution of these obstacles is of the utmost importance and will be the cornerstone for the development of new therapeutic candidates, not only for ADPKD but also for other ciliopathies.

Disclosure Statement

The authors report no conflicts of interest.

Informed Consent

This article does not contain any studies with human participants or animals performed by any of the authors.

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