Polycystic kidney disease (PKD) is a common genetic disorder in which extensive epithelial-lined cysts develop in the kidneys. In previous studies, abnormalities of polycystin protein and its interacting proteins, as well as primary cilia, have been suggested to play critical roles in the development of renal cysts. However, although several therapeutic targets for PKD have been suggested, no early diagnosis or effective treatments are currently available. Current developments are active for treatment of PKD including inhibitors or antagonists of PPAR-γ, TNF-α, CDK and VEGF. These drugs are potential therapeutic targets in PKD, and need to be determined about pathological functions in human PKD. It has recently been reported that the alteration of epigenetic regulation, as well as gene mutations, may affect the pathogenesis of PKD. In this review, we will discuss recent approaches to PKD therapy. It provides important information regarding potential targets for PKD. [BMB reports 2011; 44(6): 359-368]

INTRODUCTION

Polycystic kidney disease (PKD) is divided two types: autosomal dominant (AD) and autosomal recessive (AR). Mutations in polycystin-1 (PC-1) and polycystin-2 (PC-2) cause ADPKD; PKD is characterized by numerous cysts and fluid secretions into the lumen in the kidney (1, 2). The main cystoproteins, PC-1 and PC-2, are co-localized in primary cilia and mediate Ca²⁺ signaling as a mechanosensor (3, 4). Multiple mechanisms have been shown to be contributed to PKD, including increased proliferation and apoptosis, in addition to loss of differentiation and polarity (5). PKD causes progressive cyst formation and ultimately results in renal failure. In end-stage renal disease (ESRD) of PKD, many patients depend on hemodialysis to attenuate renal failure or transplantation, but thus far, no suitable treatment has been developed.

Recently, investigators have transferred their focus from the cause of cyst progression to the search for a target of therapy. The mammalian target of rapamycin (mTOR) pathway is the main target for a PKD therapy, because it is abundantly expressed in cyst-lining epithelial cells in human patients and mouse PKD models (6). Tuberous sclerosis complex 1 and 2 (TSC1 (hamartin) and TSC2 (tuberin)) complex have been shown to regulate mTOR signaling, and directly interact with the C-terminal cytoplasmic tail of PC-1 (6, 7). The mTOR pathway is related to cell growth; thus, mTOR inhibitors such as rapamycin (sirolimus) prevent cystic growth (6, 8, 9). Another crucial target is cAMP, which is stimulated and accumulated in the cystic fluids of PKD patients and affect diverse components of downstream signaling. Furthermore, Ca²⁺ signaling is disrupted by the mutation of PKD genes and leads to cAMP-MAPK pathway activation in PKD (10). Many cAMP-targeted drugs, such as sorafenib (BAY 43-9006) effects on cell proliferation and cystic growth and B-Raf-targeted drugs will also have to be evaluated (11, 12). Recently, metformin has been shown to reduce cystogenesis via the activation of AMP-activated protein kinase (AMPK) which inhibits two main targets; CFTR and mTOR (13). Therefore, combined therapies for the treatment of PKD still need to be studied.

Many drugs for ADPKD are currently in clinical trial stage, many of which have functional anti-hypertension, anti-proliferation and anti-inflammation effects. Clinical trials are currently underway with angiotensin I-converting enzyme inhibitor (ACEI), angiotensin II-receptor blocker (ARB), V2 vasopressin receptor (VPV2R) antagonist, somatostatin and mTOR inhibitor (14). However, it would appear that one drug alone is not fully capable of attenuating progressive cystic growth; thus, diverse approaches for the treatment of PKD still require further study.

Epigenetic regulation is defined as heritable changes in gene expression that are not attributable to any alteration in the DNA sequence. Epigenetic modulations including DNA methylation, histone modification, and gene regulation by micro RNA (miRNA) are importantly associated with several cellular processes and diverse disease states, such as cancers, even under precancerous conditions (15). The nucleosome is composed of a DNA strand surrounding a core histone octamer (16). Complicated chromatin remodeling mechanisms keep DNA accessible to transcriptional factors. Post-translational modifications including acetylation, methylation, phosphorylation, ubiquitylation, sumoylation, ADP-ribosylation, glycosylation, biotinylation and carbonylation occur in the histone...
tails (17). These epigenetic modulations alter gene activity via the regulation of DNA-histone interactions without any alteration of the genetic code (18). miRNAs, which are non-coding small 22-nucleotide RNAs, post-transcriptionally regulate the expression of target mRNAs via the 3' untranslated region (3'UTR) (19, 20). A large number of protein coding genes could be under the control of miRNAs (21, 22). As a consequence, miRNAs play an important role in the regulation of a broad variety of cellular functions, and the deregulation of miRNA expression is frequently associated with a variety of disorders, including cancer (23, 24). Recent studies have demonstrated that epigenome alterations may be involved in renal pathogenesis, including PKD, and the reversible restoration of changed epigenetic factors may improve the potential treatment of renal disease with minimal side effects (25-29).

Many current studies have attempted to devise an effective treatment; however, no preventive treatment for PKD has yet become available. A novel therapeutic approach should continue to be developed in cellular or epigenetic studies, because multiple mechanisms may contribute to PKD. This review focuses on recently described novel therapeutic approaches to the suppression of cystogenesis, specifically from a cellular or epigenetic perspective.

**NOVEL THERAPEUTIC APPROACHES IN PKD**

**Therapeutic target: PPAR-γ**

Peroxisome proliferator-activated receptor-γ (PPAR-γ) is a ligand-dependent and nuclear hormone receptor transcriptional factor, which forms a heterodimer with another nuclear receptor, retinoid X receptor (RXRα) (30). Recent studies have identified PPAR-γ as a novel target for the treatment of ADPKD. Specially, the synthetic ligands of PPAR-γ, thiazolidinediones (TZDs), are used to suppress cystogenesis and contain pioglitazone and rosiglitazone as PPAR-γ agonists (31). In an initial investigation, treatment with the PPAR-γ agonist pioglitazone improved the survival of Pkd1-/- embryos and endothelial functions of adult mice as measured by nitric oxide (NO) concentration (32). The PPAR-γ agonist rosiglitazone also affects cystogenesis, which inhibits cell proliferation in ADPKD cyst-lining epithelial cells (31). This study was conducted with the expectation that PPAR-γ agonists would attenuate cell proliferation via the checking of cell cycle molecules including PCNA, phosphorylated-Rb, and cyclin D1 and D2 (31). In a recent study, the administration of rosiglitazone was shown to attenuate cyst development and protect renal function via measurements of Blood Urea Nitrogen (BUN) and Creatinine (Cr) in a typical PKD animal model, namely the Han:SPRD rat (33). Additionally, rosiglitazone-treated Cy/+ Han:SPRD rats evidenced longer survival durations than control rats (33). In contrast, Raphael et al. reported previously that pioglitazone treatment did not result in any reduction of cystogenesis and proliferation, and only affected survival in PC-Pkd1-KO mice (34).

As interstitial inflammation and fibrosis are relevant mechanisms in the renal function of polycystic kidney, this process progressively leads to renal failure (35). TZDs have been used for the treatment of Type 2 diabetes mellitus (T2DM) because of their good safety during long-term clinical processes for the improvement of renal functions (36). TGF-β1 and MCP-1 expression was suppressed and kidney fibrosis volume and inflammatory cell infiltration were reduced by rosiglitazone treatment in PKD, as was also the case in T2DM disease (33). More recently, the novel PPAR-γ agonist known as alpha-arlyoxy-alpha-methylhydrocinnamic acid derivatives, DH9 also had anti-proliferative effects on PKD (37). Thus, PPAR-γ agonists appear to have therapeutic potential in terms of renal function; further research will be required for clinical applications.

**Therapeutic target: TNF-α**

Tumor necrosis factor (TNF) is an inflammatory cytokine and is known as a mediator of cancer-related inflammation; recently, clinical trials of cancer therapy using antagonists have been initiated (38). In PKD, TNF-α was also found to be related to the inflammation process, and were initially detected in the cystic fluids of 54 of 75 (72%) of studied PKD patients (39). Many other cytokines (interleukin (IL)-1, 2, 6, 8, ICAM-1, VCAM-1) are secreted in the fluid of the cystic kidney and may affect growth, inflammation and fibrosis in cases of PKD (39, 40). In a recent study, TNF-α has not only been associated with inflammation, but also appears to perform a crucial function in cystogenesis under both in vitro and in vivo conditions (41). They focused on FIP-2, a TNF-α induced protein that disrupts the localization of PC-2 in inner medullary collecting duct (IMCD) cells (41). It is interesting to note that TNF-α-treated embryonic kidneys have many more cyst than non-treated embryonic kidneys in Pkd2-/- and Pkd2+/- mice using organ culture systems (41). Study results have also confirmed that the TNF-α inhibitor, etanercept, reduced cyst formation for 10 weeks in Pkd2-/- mice (41). Taken together, TNF-α is a potential target in therapeutic view because it may involve in main mechanism of PKD; cyst progression and inflammatory disorder (42).

**Therapeutic target: CDK**

In the cell cycle, cyclin-dependent kinase (CDK) and the cyclin family are primarily involved in the G1/S checkpoint. Bukanov et al. previously reported the inhibition of the CDK effect on slowly progressive cystogenesis in jck and cpk mice models using roscovitine (43). Roscovitine (Seliciclib, CYC202) is a known CDK inhibitor for Cdk2-cyclin E and is in phase II clinical trials as an anti-cancer agent (44). This study showed that treatment with roscovitine resulted in dephosphorylation of Rb and a reduction in cyclin D1 levels, suggesting block G1-S phase in cell cycle in jck mice (daily dosing for 5 weeks) (43). Additionally, roscovitine affected apoptosis by checking the levels of caspases 2 and 3, ApaF1 and Bcl-2 (43). In other stud-