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Research Article

RELATIONSHIP BETWEEN SHH SIGNALING AND ADPKD

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ABSTRACT

Autosomal Dominant Polycystic Kidney Disease (ADPKD) is caused by mutations of*PKD1* or *PKD2* gene, but there is no consolidated conclusion about how these gene mutations lead to the formation of renal cysts. The *PKD1* gene and *PKD2* gene encode proteins polycystin-1 (PC1) and polycystin-2 (PC2), respectively. The PC1/PC2 protein complex is involved in several common signaling pathways. Loss of PC1/PC2 leads to abnormal signaling pathways, resulting in renal cysts formation. Shh signaling pathway regulates cell morphogenesis and differentiation, and is closely related to the function of primary cilia. Shh signaling pathway also plays an important role in the development of various tissues and organs, and abnormal expression of Shh accounts for developmental disorder. PKD cells exhibit dysregulated proliferation and aberrant ciliogenesis. This indicates that the abnormality of Shh signaling pathway is corelated to ADPKD.

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INTRODUCTION

Autosomal Dominant Polycystic Kidney Disease (ADPKD) is the most common monogenic hereditary kidney disease which is characterized by the numerous progressive, bilateral, fluid-filled cysts in the kidneys and other duct/tubule-containing organ[1-3]. ADPKD usually appears in adulthood with an incidence of 1:400-1000, and is the fourth most common single cause of end-stage renal failure worldwide [4]. Extra-renal manifestations are often prominent in individuals with ADPKD. Liver cysts occur in 83% of ADPKD patients overall, and in 94% of those older than 35 years of age[5]. 16% percent suffer from cerebral aneurysms [6]. Other phenotypes include aortic root and thoracic aorta abnormalities [7], mitral valve prolapse [8], and abdominal wall hernias [9].The most serious renal complication is end-stage renal disease (ESRD) which occurs in 50% of affected individuals by the age of 60 years.

The pathogenic gene of ADPKD are *PKD1* and *PKD2*. Approximately 85%~ 90% of ADPKD patients have mutations in *PKD1*. The remaining 10%~15% of ADPKD patients have mutations in *PKD2*.ESRD in patients with *PKD1* mutations occurs 10 years earlier than patients with *PKD2* mutations [10]. *PKD1* gene is located on chromosome 16p13 and encodes a large membrane-associated receptor-like protein, named polycystin-1 (PC1). PC1 is a large integral membrane protein (4303 amino acids), and is predicated to have 11 transmembrane domains, a large extracellular domain (3,051 aa), and a short intracellular cytoplasmic tail. The extracellular region consists of a variety of domains, including two leucine-rich repeats, a cell wall integrity and stress-response component 1 (WSC) domain, an immunoglobin-like PKD domain, a C-type lectin domain, a cysteine-riched low density lipoprotein (LDL) domain, fifteen PKD repeats, a homology to the receptor for egg jelly (REJ) domain and a potential proteolytic cleavage site (GPS domain). Within the first transmembrane domain, there is a region of similarity to lipoxygenases (PLAT domain). The carboxyl-terminus located in the cytoplasm is consisted of 226 amino acids and contains several potential sites of phosphorylation and a coiled-coil domain that mediates protein-protein interactions[11].

*PKD2*genemaps to chromosome4q21 and encodes a membrane-associated protein designated polycystin-2 (PC2)[12]. PC2is composed of 968 amino acids with 6 transmembrane domains, an intracellular amino- and a carboxyl-termini. The carboxyl-terminal domain also contains a coiled-coil segment, and a motif known as an EF hand which bind calcium[13]. PC2 is deemed to be a nonselective cation channel that transports calcium. Because PC2 have the similar amino acids and shares structural features with transient receptor potential (TRP) channels as well as voltage-activated calcium and sodium channels, it is thought to be a member of TRP family, named TRPP2[14, 15]

Previous reports demonstrated that PC1 and PC2 physically interact with each other via their intracellular COOH termini [16]and the resulting complex, calledthe TRPP1/2 channel

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complex, is thought to consist of three PC2 subunits and one PC1 subunit [17].These results suggest that the large extracellular segment of PC1 could be the receptor, whereas its intracellular and cytoplasmic segments mediate with PC2 to form TRPP1/2 channel complex.

In general, functional loss of PC1 or PC2 protein would lead to aberrant ion secretion, planer cell polarity, and gene transcription[18].These anomalies involve in diverse signaling pathways, such as mTOR, cAMP, Wnt which underlying the molecular mechanism of cystogenesis. It is currently believed that PC1/PC2 is localized to the cilia of renal epithelial cells, and changes in cilia formation and abnormal cilia may cause renal cyst formation[19-22].

Primary cilium is a microtubule-based organelle that not only playsmultiple roles in cell motility but also transmits signals to the cytoplasm and nucleus regulating cell function, gene expression, development [23]. Shh signaling pathway is closely related to normal function of primary ciliumand abnormal shh signaling resultsin defective ciliogenesis, ciliary dysfunction and ciliopathy[24].

Hedgehog (Hh)

Hedgehog (Hh) was first identified by genetic screens in *Drosophila melanogaster*[25]. This name derives from the appearance of embryos with null alleles of Hh, which display a lawn of disorganized, hair-like bristles reminiscent of hedgehog spines. In the early 1990s, three Hh gene homologs were discovered in vertebrates, which are Sonic Hedgehog (Shh), Indian Hedgehog (Ihh), and Desert Hedgehog (Dhh) respectively [26]. Dhh and Ihh have been shown to play important roles in normal tissue development, including pancreas and testis organogenesis and bone formation [27]. Among mammalian Hedgehog genes, the mechanism of Shh is most intensively investigated. Shh is highly evolutionarily conserved and is the most potent of these ligands and is the most widely expressed in adult tissues such as notochord, neural tube, intestine, and limbs. Shh signaling plays an essentialrole in embryonic development and is critical for maintenance of tissue polarity.

Hedgehog family proteins are synthesized as ~45-kD precursorproteins that undergo an intramolecular cleavage and yields a 25-kD C-terminalfragment and an ~19-kD N-terminal fragment[28]. The N-terminal domain involves the signal activity of the Shh protein, while the C-terminal domain has autoproteolytic enzyme activity and cholesterol transferase activity. In secretory cells, cholesterol molecules direct the transfer process of Shh protein. The Shh precursor protein is cleaved into the N-terminus and the C-terminus by autocatalysis in the endoplasmic reticulum. The C-terminus covalently binds to the cholesterol molecule and transfers it to the N-terminus domain where the cysteine is palmitoylated resulting from the catalyzation of acyltransferase[29]. Shh proteinsexert their biological functions through these post-translational modifications. Shh signaling pathway plays pivot role in organogenesis of mammalian. Abnormality of shh will lead to severe congenital malformations, including kidney malformations. In clinics, patients with Shh gene mutation manifest as kidney dysplasia or genitourinary malformation[30].

Hedgehog signaling pathway can be divided into canonical and non-canonical pathway. The canonical Hedgehog pathway contains several key components, including Hh glycoproteins Shh, Ihh, and Dhh[31]. Upon secretion, Shh glycoproteins bind and inactivate the 12-transmembraneprotein Patched1 (Ptch1), which normally inhibits the activity of the 7-transmembrane protein Smoothened (Smo). In the presence of Shh ligand, Ptch1 inhibition of Smo at the primarycilium is abrogated resulting in the nuclear localization of glioma-associated (Gli) transcription factors, which are the terminal effectors of the Shh signaling. In vertebrates, there are three Gli transcription factors (Gli1, Gli2 and Gli3). Gli1 is the only full-length transcriptional activator whereas Gli2 and Gli3 act aseither positive or negative regulators as determined by posttranscriptional and posttranslational processing [32]. In response to Shh ligand binding, Gli2 accumulates in the primary ciliumand drives transcriptional activation, overcoming negative regulation by Gli3[33]. Gli transcription factors can activate target genes that includestargets involved in Hh pathway feedback (e.g., *Gli1*, *Ptch1*), proliferation (e.g., *Ccnd1*, *Myc*), apoptosis (e.g., *Bcl-2*), angiogenesis (e.g., *Ang1/2*), epithelial-to-mesenchymal transition (e.g., *Snail*),and stem cell self-renewal (e.g., *Nanog*, *Sox2*)[34].

In addition to the classical signaling pathway, there are also non-canonical path ways related to Shh signaling. Non-canonical Shh signaling refers to either: (1) activation of signaling from Ptch1/Smo but independent of Gli transcription factors; or (2) activation of Glitranscription factors independent of Shh ligand or Ptch1/Smo. The latter is better studied and multiple pathways have been identified, mostly oncogenic, that can increase Gli activity. Glitranscription factors have been shown to be positively regulated by K-Ras, TGF-β, PI3K-Akt, and PKC-α [35-37].

During kidney development, the Shh signaling pathway directly affects the expression of three different genes: early renal induction model genes (*Pax2, Sall1*), cell cycle regulators (*Ccnd1, N-myc*) and hedgehog signaling pathway effect or (*Gli1, Gli2*). In the kidney of mouse embryos, Shh is specifically expressed in distal epithelial cells of the ureter and medullary collecting duct [38]. Shh germline mutations results in embryonic lethality or severe developmental malformations, including renal dysplasia, single kidney, ectopically developed abnormal kidneys[39, 40].

Shh signaling pathway also plays essential role in the formation of ureter. Inhibition of Shh signaling pathway in urothelial cells leads to ureteral hydronephrosis and hydronephrosis. Loss of Shh will attenuate smooth muscle differentiation and urinary pacemaker cell development; in contrast, over expression of Shh attenuates urocaptopocyte function[38].

Many studies have demonstrated that primary cilia are closely related to the Shh signaling pathway. In mammalian cells, the Shh signaling pathway components Ptch, Smo and its downstream transcription factors Gli1, Gli2 and Gli3 are present on the primary cilia. In the absence of Shh, Ptch concentrates on primary cilia, preventing Smo from accumulating in the primary cilia. When Shh is present, Shh binds to Ptch, and Ptch leaves the primary cilia, causing Smo to accumulate in the primary cilia, thereby initiating expression of downstream genes. When the primary cilia structure or

function is abnormal, the Shh signaling pathway cannot function normally, and dysplasia or other diseases occur. In addition, PC1/PC2 is localized to the primary cilia of renal epithelial cells. These cilia localization changes and cilia abnormalities may lead to the formation of renal cysts, while primary cilia play a key role in the pathogenesis of ADPKD. ADPKD cells exhibitabnormal proliferation manifested the lack of normal function of cilia. The abnormality of morphology and number of primary cilia of ADPKD renal epithelial cells indicated that the dysfuction of Shh signaling pathway was associated with ADPKD.

Despite the connection between primary cilia and Shhsignaling is palpable, a role for Shh signaling in cystic kidney disease has notbeen studied extensively. Yet the few studies implicating Shhsignaling in cystic kidney disease are quite compelling. First, Hu *et al*. found that 50%of Shh-nullmouse embryos formed a single, ectopic and dysplastic kidney [40]. Second, loss of the transcription factor, Glis2, a member of the Kruppel-like C2H2 zinc finger protein subfamily, which includes the Gliproteins, resulted innephronophthisis in humans and mice[41].Third, transcripts of Hedgehog targetgenes increased in cystic kidneys of two orthologous mouse mutants, *jck* and *Pkd1*, and Hedgehog inhibitors reduced cystogenesis in *jck* and *Pkd1* cultured kidneys[42].

Recently, a newly published paper showed that in human ADPKD tissue, Hedgehog target and activator, Glioma 1, was elevated and localized to cyst-lining epithelial cells and to interstitial cells, suggesting increased autocrine and paracrine Hedgehog signaling in ADPKD, respectively. Hedgehog inhibitors reduced basal and cAMP-induced proliferation of ADPKD cells and cyst formation *in vitro*. These data suggest that Hedgehog signaling is increased in human ADPKD and that suppression of Hedgehog signaling cancounter cellular processes that promote cyst growth *in vitro*[43]. Thus, enhanced Hedgehog activity may have a general role in renal cystogenesis and thereby present a novel therapeutic target.

An increasing number of researches indicate that primary cilia and Shh signaling pathway are closely related to human development, health and disease. With the gradual understanding of primary cilia structural function and Shh signaling, the role of primary cilia and Shh signaling pathway has been paid increasing attention in the study of the pathogenesis of ADPKD, especially in recent years by targeted inhibition of the Shh signaling pathway. However, the current research on the relationship between ADPKD and Shh signaling pathways needs further exploration.

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