ARC Journal of Nephrology
Volume 3, Issue 1, PP 13-18
www.arcjournals.org

Wnt Signaling Pathway in Polycystic Kidney Disease

Ao Li*

Department of Pharmacology, Yale University School of Medicine, New Haven, CT 06520, USA

***Corresponding Author:** ***Ao Li**, Department of Pharmacology, Yale University School of Medicine, New Haven, CT 06520, USA, **Email:** ao.li@yale.edu*

Abstract: *Wnt signaling involves a variety of signaling cascades that can be activated by secreted Wnt ligands. Two major Wnt pathways, the canonical or β-catenin pathway and the planar cell polarity (PCP) pathway, have recently been demonstrated that plays important roles in multiple cellular processes within the kidney. Both of these pathways are essential for kidney development as well as homeostasis and injury repair. The disruption of Wnt pathway will result in cystic kidney disease, a group of genetic diseases that includes the most common hereditary life-threatening syndrome polycystic kidney disease (PKD). Recent studies implicate canonical and noncanonical Wnt pathways in cystogenesis and points to a remarkable role for developmental processes in the adult kidney.*

Keywords: *Wnt Signaling, Polycystic kidney disease*

1. Polycystic Kidney Disease

Polycystic kidney disease (PKD) is an inherited disorder in which the renal tubules become structurally abnormal, resulting in the development and growth of multiple cysts within the kidney (1). These cysts may begin to develop before birth or in infancy, in childhood, or in adulthood (2). Cysts are non- functioning tubules filled with fluid pumped into them, which range in size from microscopic to enormous, crushing adjacent normal tubules and eventually rendering them non-functional also. The two main types of polycystic kidney disease are: autosomal dominant polycystic kidney disease (ADPKD) and autosomal recessive polycystic kidney disease (ARPKD).

Autosomal dominant polycystic kidney disease (ADPKD) is the most common of a group of inherited kidney disorders characterized by progressive cyst development and various extrarenal manifestations (3, 4). Cystogenesis in human kidneys progressively occupy the normal parenchyma of the kidney and lead to renal failure, which usually occurs in mid-to-late adulthood. This disease is the fourth most common single cause of end-stage renal failure worldwide (5, 6).

ADPKD is caused by mutations in the PKD1 or PKD2 genes, which encode the proteins polycystin-1 (PC1) and polycystin-2 (PC2), respectively. Approximately 85% of ADPKD patients have mutations in PKD1, and the remaining 15% have mutations in PKD2 (7, 8). The most common extra renal manifestation of ADPKD is the formation of bile-duct-derived cysts in the liver (4, 9). Liver cysts occur in 83% of all ADPKD patients, and 94% of the patients with liver cysts are over 35 years old (10, 11). Other ADPKD phenotypes include pancreatic cysts (12, 13), aneurysms (14-17), and aortic root/thoracic aorta abnormalities (18-20).

Autosomal recessive polycystic kidney disease (ARPKD) is one of the most common hereditary renal cystic diseases in infants and children, with an estimated incidence of ~1 in 20,000 live births and a prevalence of heterozygous carriers of ~1 in 70 (21, 22). The disease is caused by mutations in PKHD1, which encodes a 16-kb transcript, contains at least 86 exons, and spans 470 kb on chromosome 6p12 (23). The longest ORF is predicted to be 66 exons and yields a 4074-amino acid membrane-associated receptor-like protein, fibrocystin/polyductin (FPC) (24-28). Its major clinical manifestations include fusi form ectasia of the renal collecting and hepatic biliary ducts and fibrosis of the liver and kidneys (29-31), although the renal lesions predominate at the time of diagnosis (31, 32). Approximately 50% of ARPKD patients present as neonates (33) when they are born with dramatically enlarged, symmetric kidneys and ectasia of the collecting duct (34, 35). The mortality rate is 30-50% for neonates due to respiratory and/or renal dysfunction (36).

2. Wnt Signaling Pathway

Wnt protein family is a class of highly conserved evolutionarily secreting glycoproteins involved in cell proliferation, survival, differentiation, polarity,

cell fate determination in embryonic development and homeostasis of adult tissues (37). Wnt signaling pathway includes the canonical Wnt/β-catenin signaling pathway and non-canonical pathway (38). In the canonical Wnt pathway, two cell membrane proteins, Frizzled (FZD) and LDL-receptor related protein 5/6 (LRP5/6), function together as receptors for the Wnt ligands. In the absence of a Wnt signal, β-catenin is continuously phosphorylated by a multiprotein destruction complex, which includes Axin, adenomatous polyposis coli (APC), casein kinase 1α (CK1α) and glycogen synthase kinase 3β (GSK3β). Phosphorylated β-catenin is targeted for proteasomal degradation. As soon as Wnts binds to their receptors Frizzled and LRP5/6, the destruction complex function becomes disrupted, which in turn promotes β-catenin accumulation and translocation to the nucleus. In the nucleus, β-catenin forms a complex with TCF/LEF transcription factors that regulate target gene transcription such as Cyclin D1, c-Jun, c-Myc (39).

Non-canonical Wnt signaling pathway mainly refers to Wnt/Ca2+ signaling pathway and Wnt/PCP signaling pathway. Non-canonical Wnt signaling controls cell polarity through activation of RhoGTPase or via β-catenin-independent mechanisms to increase intracellular Ca2+ concentration. Wnt/PCP pathway regulates small GTPaseRhoA and c-Jun N-terminal kinase (JNK), activates RhoGTPase to cause cytoskeleton and microtubule convergent extension which is crucial for cell shape and adhesion function of epithelial cells. Wnt/Ca2+ pathway regulates the movement of cells in the early stages of development. Frizzled appears to activate phospholipase C and phosphodiesterase to increase cells intracellular calcium and reduce intracellular cyclic guanosine (cGMP) concentrations (40). Canonical and non-canonical Wnt signaling are involved in the regulation of kidney development development as well as homeostasis and injury repair (41).

3. PKD AND WNT SIGNALING

There has been considerable progress in elucidating the molecular mechanisms and pathogenesis of ADPKD (5, 7, 42-44). Previous studies showed that human cystic disease may involve Wnt signal transduction (41, 45, 46). In the kidney, canonical Wnt signaling is indispensible for induction of the metanephric mesenchyme and ureteric bud branching. The noncanonical Wnt signaling regulates planar cell polarity, cell migration and mitotic spindle orientation. These processes are critical for proper tubular morphology. Hitherto, many reports have demonstrated that renal cystic disease may result from dysregulation of non-canonical Wnt pathway by disrupting Wnt/Ca2+ signaling and/or PCP processes in renal epithelial cells (47-51).

For example, Kim et al., found that Wnts bind to the extracellular domain of polycystin-1 and induce whole-cell currents and Ca2+ influx dependent on polycystin-2. Mutations of either polycystin-1 or polycystin-2 that disrupt complex formation, compromise cell surface expression of polycystin-1, or decrease polycystin-2 channel activity suppress activation by Wnts. Pkd2-/- fibroblasts lack Wnt-induced Ca2+ currents and are unable to polarize during directed cell migration (47). Meanwhile, result from Luyten group indicated that cystic kidneys exhibited remarkable up regulation and activation of Frizzled 3 (Fz3), a regulator of PCP, and its downstream effector, CDC42. Fz3 was expressed on the cilia of cystic kidneys but barely detected on the cilia of normal kidneys. In vitro, polycystin-1 and Fz3 antagonized each other to control CDC42 expression and the rate of cell migration in HEK293T cells. All their data suggested that polycystin-1 controlled oriented cell division and that aberrant PCP signaling contributed to cystogenesis.

In spite of these findings, functional roles of canonical Wnt signaling in pathogenesis of ADPKD remain to be unequivocally defined. A transgenic mouse for β-catenin, a key factor for canonical Wnt signaling, exhibited severe PKD phenotypes, showing that β-catenin up regulation alone was sufficient to induce cyst formation in the kidney (52). These mice developed severe polycystic lesions soon after birth that affected the glomeruli, proximal, distal tubules and collecting ducts. This phenotype was similar to the human ADPKD phenotype. Cyst formation was associated with an increase in cell proliferation and apoptosis. The cell proliferation and apoptotic indexes was increased 4-5-fold and 3-4-fold, respectively, in cystic tubules of the transgenic mice compared to that of littermate controls. Their findings provided experimental genetic evidence that activation of the Wnt/β-catenin signaling pathway causes polycystic kidney disease and supported the view that dysregulation of the Wnt/β-catenin signaling was involved in its

pathogenesis. Another research group also demonstrated that overexpression of c-Myc, a canonical Wnt targeting product, also induced cystogenesis in the kidney of mouse models (53). This phenotype appeared to result from the overexpression of c-Myc in the renal tubular epithelium and consequent abnormal cell proliferation. These animals reproducibly developed PKD and died of renal failure. Furthermore, Qian et al., found that disruptions of Apc, which was a co-factor for the β-catenin degradation complex, promoted cyst formation in the kidney (54). They generated mice carrying a conditional deletion of the Apc tumor suppressor gene specifically in the renal epithelium. Loss of Apc accounted for upregulation of β-catenin protein in renal epithelium. Most of these mice died shortly after birth, and multiple kidney cysts were found upon histological examination. This result illustrated that Wnt/β-catenin signaling played essential role in renal development and provided evidence that dysregulation of the pathway can initiate tumorigenesis in the kidney.

Moreover, results from our and other groups suggested that aberrantly activating canonical Wnt signaling could be detected in spectrum of Pkd1- and Pkd2-deficient cells and tissues (49, 55, 56). The polycystin- 1 C-terminal inhibited the ability of both β-catenin and Wnt ligands to activate T-cell factor (TCF) - dependent gene transcription. DNA microarray analysis revealed that the canonical Wnt signaling pathway was activated in ADPKD patient cysts, suggesting that increased canonical Wnt signaling involved in cyst formation. Our previous data also confirmed that loss of polycystin-2 disrupted normal behavior of renal epithelial cells through dysregulation of β-catenin-dependent signaling. Mutation of Pkd2 resulted in cystogenesis and upregulated β-catenin expression. These findings directly or indirectly supported that hyperactivated canonical Wnt signaling may cause cyst formation in the kidney of animal models.

However, other reports indicated that increased canonical Wnt signaling may not play a key role in cystogenesis of PKD (50, 57-60). The opposite effect has been interpreted by which cyst formation might disturb Wnt/PCP homeostasis via losing balance between the canonical and non-canonical Wnt activity (45, 48, 49, 61-63).

To directly reveal functional role of canonical Wnt signaling in cystogenesis of ADPKD, we employed a standardized mouse ortholog of human ADPKD (44) to investigate the importance of β-catenin in ADPKD phenotypes. Our data demonstrated that the elevated β-catenin signaling caused by polycystin-2 deficiency contributed to disease phenotypes in our mouse ortholog of human ADPKD. Pharmacologically inhibiting the β-catenin stability or the production of mature Wnt protein, or genetically reducing the expression of Ctnnb1 (which encodes β-catenin), suppressed the formation of renal cysts, improved renal function, and extended survival in ADPKD mice (64).

4. Conclusion and Perspective

Polycystic kidney diseases have been linked to aberrant Wnt signaling. Disruptions of cystic disease genes account for dysregulation of Wnt signaling in model organisms and cultured cells. Inappropriate levels of Wnt signaling result in renal cyst formation in mice. These observations have prompted the idea that abnormal Wnt signaling may implicate a common causative event in cyst formation. Wnt pathway has become a potential avenue for urgently required novel therapeutics for treating human kidney diseases.

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Citation: *Ao Li. Wnt Signaling Pathway in Polycystic Kidney Disease. ARC Journal of Nephrology. 3(1):13-18.*