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Wnt Signaling in Kidney Development and Disease

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Abstract

Wnt signal cascade is an evolutionarily conserved, developmental pathway that regulates embryogenesis, injury repair, and pathogenesis of human diseases. It is well established that Wnt ligands transmit their signal via canonical, β -catenin-dependent and noncanonical, β -catenin-independent mechanisms. Mounting evidence has revealed that Wnt signaling plays a key role in controlling early nephrogenesis and is implicated in the development of various kidney disorders. Dysregulations of Wnt expression cause a variety of developmental abnormalities and human diseases, such as congenital anomalies of the kidney and urinary tract, cystic kidney, and renal carcinoma. Multiple Wnt ligands, their receptors, and transcriptional targets are upregulated during nephron formation, which is crucial for mediating the reciprocal interaction between primordial tissues of ureteric bud and metanephric mesenchyme. Renal cysts are also associated with disrupted Wnt signaling. In addition, Wnt components are important players in renal tumorigenesis. Activation of Wnt/ β -catenin is instrumental for tubular repair and regeneration after acute kidney injury. However, sustained activation of this signal cascade is linked to chronic kidney diseases and renal fibrosis in patients and experimental animal models. Mechanistically, Wnt signaling controls a diverse array of biologic processes, such as cell cycle progression, cell polarity and migration, cilia biology, and activation of renin–angiotensin system. In this chapter, we have reviewed recent findings that implicate Wnt signaling in kidney development and diseases. Targeting this signaling may hold promise for future treatment of kidney disorders in patients.

1. INTRODUCTION

Wnt signaling is one of the most highly conserved pathways throughout evolution, and it plays important roles in a diverse array of biologic processes, such as embryonic development, metabolism, tumorigenesis, and stem cell renewal.^{1–3} The first *Wnt-1* gene, also known as *Wingless* in *Drosophila* and *Int-1* in mammals, was discovered based on the activation by integration of virus DNA in mouse breast tumors in 1982.⁴ Sequence analyses revealed that *Wnt-1* was actually the homolog of the *Wingless* (*wg*) gene in *Drosophila* that controls segment polarity in the formation of the body axis during

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embryonic development. Since then, totally 19 Wnt ligands in mammalian genomes are identified, which possess unique structural features and distinct expression patterns. The signal is initiated through the engagement of Wnt ligands to the extracellular domain of frizzled (Fzd) receptor and coreceptors, the low-density lipoprotein receptor-related protein 5 and 6 (LRP5 and LRP6).⁵ Depending on the involvement of key intracellular molecule β -catenin, Wnt signaling is typically classified as either β -catenin-dependent, canonical or β -catenin-independent, noncanonical pathways. The latter includes Wnt/planar cell polarity (PCP) and Wnt/ Ca^{2+} signaling routes.^{5–7}

Wnt ligands and their receptors are expressed in developing kidney during nephron formation.^{8,9} Although this signal is relatively silent in adult, it becomes reactivated rapidly after a wide variety of injuries.^{10–12} In the past decades, tremendous efforts have been made to delineate the expression, function, and targets of Wnt/ β -catenin signaling in the developing kidneys, as well as in damaged kidneys after injury.^{6,13} In this chapter, we provide a comprehensive review on the expression, regulation, and function of Wnt/ β -catenin signaling in the context of kidney development and disorders.

2. WNT SIGNALING: COMPONENTS AND ROUTES

The canonical pathway of Wnt signaling is mediated by intracellular protein β -catenin (Fig. 1). In the absence of Wnt ligands-receptors engagement, cellular β -catenin levels are limited due to the phosphorylation-triggered proteasome degradation (Fig. 1A). Upon activation, Wnt ligands bind to the Fzd and LRP5/6 receptors, thereby activating the cytoplasmic protein dishevelled (Dvl). Dvl then inhibits the β -catenin destruction complex, consisting of the scaffold proteins Axin, adenomatous polyposis coli (APC), serine/threonine kinases of glycogen synthase kinase-3 β (GSK-3 β), and casein kinase 1 (CK1). Unphosphorylated β -catenin accumulates in the cytoplasm and enters the nucleus, where it interacts with T cell factor (TCF)/lymphoid enhancer-binding factor (LEF) family of transcription factors to regulate Wnt target genes (Fig. 1A).¹⁴

Recent studies indicate that pro(renin) receptor (PRR) may function as an amplifier of the canonical Wnt/ β -catenin signaling (Fig. 1A).¹⁵ PRR is a transmembrane protein with multiple distinct functions.¹⁶ We reported that PRR is an essential component of the Wnt receptor complex and is obligatory for its signal transduction. Meanwhile, Wnt/ β -catenin controls PRR gene and induces its expression in kidney tubular epithelial cells. Therefore, PRR induction and Wnt/ β -catenin activation constitute a self-perpetuating cycle, which leads to the amplification of Wnt/ β -catenin signaling.^{15,17}

Wnts are also able to transmit their signals via β -catenin-independent, noncanonical pathways (Fig. 1B–C).^{3,6} The Wnt/PCP pathway is evolutionarily conserved and plays a major role in embryonic tissue patterning, cell polarization, migration, and morphogenesis (Fig. 1B).¹⁸ The Wnt/PCP ligands, such as Wnt5, Wnt7, and Wnt11, bind to the 7-transmembrane Fzd receptor and then recruit the cytoplasmic scaffold protein Dvl to the plasma membrane. Additional downstream components of the Wnt/PCP pathway include Van Gogh homolog 2 (Vangl2), Celsr1, Prickle, protein tyrosine kinase 7 (Ptk7), and Scrib, which work together to establish planar polarity. The Wnt/PCP effectors then regulate

cytoskeleton dynamics directing asymmetric distribution of cellular components and migration. Many targets, such as Daam1, Rho, Rac, Rho kinase, C-Jun N-terminal kinase (JNK) are involved in these final steps (Fig. 1B).¹⁹

Another noncanonical Wnt signaling is the Wnt/Ca²⁺ pathway, which leads to the release of intracellular Ca²⁺, possibly via G-proteins (Fig. 1C).^{3,6} This pathway involves activation of phospholipase C (PLC) and protein kinase C (PKC). Elevated Ca²⁺ can activate the phosphatase calcineurin, which leads to dephosphorylation of the nuclear factor of activated T-cells (NFAT) and its accumulation in the nucleus (Fig. 1C). The Ca²⁺-mediated pathway has critical roles in dorsal/ventral patterning, gastrulation, and cardiac development. While the involvement of Wnt/ β -catenin and Wnt/PCP signaling in regulating kidney development and disease is well studied, little is known about the role of Wnt/Ca²⁺ pathway in these processes.

3. WNT SIGNALING AND KIDNEY DEVELOPMENT

3.1 Major Events in Nephrogenesis

Significant advances have been made in deciphering molecular events in kidney development, making it possible to recognize the temporal and spatial pattern of embryonic kidney and its progenitors (Fig. 2).²⁰ The mammalian kidney originates from intermediate mesoderm (IM) after gastrulation, and then lies along the anteroposterior axis between paraxial mesoderm and IM.²¹ There are three stages of kidney development in a temporal and craniocaudal sequence, and each is marked by the successive development of a more advanced kidney: pronephros, mesonephros, and metanephros (Fig. 2). The pronephros, also named primitive kidneys, develops at embryonic day 8.5 (E8.5) in a mouse embryo and at approximately the sixth somite in humans, and consists of 6–10 pairs of tubules.²² This organ is considered as transient structures in mammals and completely disappears, but it is essential for the next coming cells and tissues, including the mesonephric kidney. The mesonephros, also named middle kidney, develops by the formation of mesonephric tubules from the IM and is physiologically functional during early embryonic life with the structure of mesonephric tubules and ducts [Wolffian ducts (WD)] at E10 in mouse embryo. The mesonephric duct reaches the cloaca with the proximal end and convoluted tubules blending into the duct. An important aggregate adjacent to the duct is called the metanephric mesenchyme (MM). The mesonephros gradually degenerates, but it also contributes to other organs, such as reproductive tracts of the testes, epididymal ducts, and vas deferens in all vertebrates. The metanephros, also named permanent kidney, begins in week 5 of gestation in humans and at E10.5 in mice. Metanephros is also derived from the IM, and finally becomes the functional adult kidney in mammals (Fig. 2).²³

The process of metanephric nephrogenesis is initiated by the invasion and reciprocal interaction between the ureteric bud (UB) and MM.²⁴ The UB arises from an outgrowth of the Wolffian duct and invades the MM, and induces the surrounding mesenchyme to undergo a mesenchymal to epithelial transition (MET), further forming the renal vesicles (RVs). The RVs subsequently differentiate through comma- and S-shaped body stages, and give rise to glomerular podocytes, parietal epithelium cells, proximal, and distal tubule cells²⁵; whereas

the UB undergoes branching morphogenesis to form collect duct. As such, the metanephros finally gives rise to ureteric tree and mature kidney.²⁶

3.2 Wnt Ligands and Nephron Formation

Wnt signaling plays critical roles in several processes during kidney development, such as UB induction and nephrogenesis (Table 1).²⁷ Using β -catenin responsive TCF/ β -gal reporter mice (Fig. 3A),²⁸ canonical Wnt signaling activation was detected in the epithelia of branching UB and MM.²⁹ This signal is quickly decreased in mature nephrons and disappeared in postnatal kidney. The Wnt inhibitor, Dickkopf-1 (Dkk1), could disrupt UB growing in cultured fetal kidney explants, which confirms the intense canonical Wnt signaling in branching nephrogenesis.²⁹ Active β -catenin signal is detectable within the mesenchymal progenitor pool of RVs in mice, which is both necessary and sufficient to regulate RVs and induces the expected molecular responses.³⁰ Both microarray and genetic analysis revealed that there is Wnt-dependent pathway regulated by protein kinase A (PKA) via Wnt induction during progression of the MM to tubular differentiation.³¹ Wnt signaling also patterns the proximal-distal nephron axis through enriching in the distal and decreasing in the proximal region of the forming nephron in chick models.³² It is concluded that high Wnt levels induce tubular components, whereas areas with low level of Wnt ligands give rise to glomerular elements.³²

Deficiencies in Wnt ligands have been linked to serious renal developmental defects.³³ The first significant observation indicates that Wnt1 could replace UB for the induction of tubulogenesis.³⁴ Thus far, a total of 7 Wnt ligands have been found during kidney ontogeny, including Wnt2b, Wnt4, Wnt5a, Wnt6, Wnt7b, Wnt9b, and Wnt11 (Table 1).^{35,36} Wnt2b and Wnt4 are expressed in the kidney mesenchymal cells.^{37,38} Studies suggest that Wnt4 plays central roles in the initial stages of renal development,³⁹ and it does so by both canonical and noncanonical pathways.^{40,41} Furthermore, Wnt4 is able to coordinate with bone morphogenetic protein 4 (BMP4) to regulate the smooth muscle cells in medullary stroma for renal vascular development and maturation.⁴² Patients with a *Wnt4* mutation are associated with Müllerian-duct regression and renal defects.^{43,44}

Wnt5a is also critical for early kidney development, as suggested by recent studies.⁴⁵ Wnt5a is shown to act through Ror2 for the induction of metanephric mesenchyme and renal morphogenesis via a noncanonical pathway.^{46,47} Mutation of *Wnt5a* could lead to urogenital defects of the congenital anomalies of the kidney and urinary tract (CAKUT), which disrupts multiple tissue differentiation and development.⁴⁸ Wnt6, Wnt7b, Wnt9b, and Wnt11 are all expressed in the UB during the early stages of development. Aside from its role in UB branching morphogenesis, Wnt6 could rescue the Wnt4 mutant embryos and upregulate Wnt4 transcription for ureter epithelialization.⁴⁹ Wnt7b acts in cortico-medullary axis, and embryonic kidneys fail to form medullary zone and are unable to concentrate urine normally in Wnt7b^{-/-} null mice.⁵⁰

Wnt9b is one of the major ligands in the organization of mammalian urogenital system.⁵¹ The Wnt9b-expressing cells functionally act for the inductive response in metanephric mesenchyme, which is critical for the development of mesonephric/metanephric tubules and extension of the Müllerian duct.⁵¹ In order to keep the balance between maintenance of renal

mesenchymal progenitor and mesenchymal to epithelial transition (MET) differentiation, *Wnt9b* controls subsets of progenitor cell's state for differentiation or undifferentiation.⁵² Further evidences demonstrate that active *Wnt9b*/β-catenin signaling in *Six2* positive progenitors is required for their renewal/proliferation.⁵² The transgenic mice with overexpression of *Wnt9b* in *Six2* lineage display a disrupted cell fate decisions and severe renal defects, such as CAKUT.⁵³ After deletion of β-catenin specifically in the kidney stroma, the fibroblasts in kidney capsule, cortex, and medulla, the expression of *Wnt9b* was markedly reduced in adjacent ureteric epithelial cells, suggesting the role of *Wnt9b* as effector downstream of β-catenin during induction of nephron progenitors.⁵⁴ It is interesting to note that *Wnt9b* participates in the planar cell polarity of epithelium and contributes to the size of tubular diameters. The mice with attenuation of *Wnt9b* exhibit randomly oriented cell divisions and significantly increase tubular diameter, which act through the noncanonical Rho/JNK pathway during kidney morphogenesis.⁵⁵

Wnt11 was first identified to be expressed in the nephric duct prior to the outgrowth of UB in control of its branching.⁵⁶ This expression is independent of *Wnt4* and MM specific factors, suggesting that it acts as an autocrine factor inside the ureteric epithelium.⁵⁶ The *Wnt11* gene in human embryos displays its restricted expression in the tips of the UB. There is an important feedback loop among *Wnt11*, Ret tyrosine kinase receptor, and glial cell-derived neurotrophic factor (GDNF).⁵⁷ Deficiency of the *Wnt11* gene disrupted the UB branching morphogenesis and led to renal hypoplasia in embryonic mice, which was rescued by maintaining GDNF expression.⁵⁷ Furthermore, *Wnt11* expression is reduced in the absence of Ret/GDNF signaling.⁵⁷ These results illustrate the synergistic interaction of *Wnt11*/GDNF/Ret and their positive autoregulatory mechanism during normal ureteric branching morphogenesis. The role of *Wnt11* in later stage of mammalian kidney organogenesis is established and supported by the anomalies in kidney tubular system and secondary glomerular cysts in *Wnt11*^{-/-} null mice, which is consistent with its early involvement in UB branching.⁵⁸ These effects presumably act through several downstream genes implicated in kidney development, such as *Wnt9b*, *Six2*, *Foxd1*, *Hox10*, and *Dvl2*.⁵⁸

3.3 Wnt Signaling Effectors and Kidney Development

Our previous studies exhibit that the key Wnt coreceptor LRP6 plays critical roles during early kidney development.⁵⁹ The *LRP6* knockout mice exhibit severe urogenital defects with hypoplasia cystic kidney (Table 1). Further studies reveal that the UB inductive factor of Ret acts downstream of LRP6-mediated Wnt signaling, which is most likely responsible for renal defects in mutant mice.⁵⁹ After inhibition of *Xenopus frizzled-8* (*Xfz8*), one of the Fzd receptor of Wnts, defects in pronephric tubule branching are evident, suggesting a role for *Xfz8* in maintaining normal epithelium structure of pronephric duct and tubules.⁶⁰ The phenotypes of targeted mutations in *Fzd4* and *Fzd8* result in disrupted UB growth and reduction of kidney size, but there might be homeostatic network regulations in the mutants of *Fzd4*^{-/-} or *Fzd4*^{-/-}; *Fzd8*^{-/-} cells compared with wild-type controls, which can account for discrepancies in renal phenotypes.⁶¹ Through inhibition of GSK-3β, the Wnt agonist lithium is able to induce early stages of epithelial differentiation in isolated nephrogenic mesenchyme, indicating the possible molecular mechanisms in the early events of nephrogenesis.⁶² These results are further confirmed by independent group using GSK-3β

inhibitor lithium or 6-bromoindirubin-3'-oxime (BIO), which result in abundant epithelial differentiation and full segregation of nephrons.⁶³ Furthermore, stabilized β -catenin and upregulated LEF1 and TCF1 are capable of inducing nephron differentiation in isolated kidney mesenchymes as well.⁶³

As β -catenin is the principal intracellular mediator in canonical Wnt signaling, more attentions have been paid to elucidate its roles during kidney development. Active form of β -catenin is detectable as early as E6.5 in mouse embryo, and contributes to anterior–posterior axis, primitive streak, and mesoderm formation.⁶⁴ In vitro and in vivo studies indicate that Six2-dependent self-renewal and β -catenin-directed differentiation institutes a regulatory complex, which keeps the balance between nephron progenitor maintenance and nephrogenesis.⁶⁵ Conditional deletion of β -catenin in mouse WD epithelium with Hoxb7-Cre causes defect in branching morphogenesis and results in renal aplasia or hypoplasia.⁶⁶ Multiple putative targets of β -catenin/TCF transcripts, such as cyclin D1 and Emx2, are detected along renal epithelial differentiation in organ culture of rat embryonic kidney.⁶⁷ In order to delineate the role of β -catenin at the late S-shaped body stage, mice with conditional deletion of β -catenin was created in the developing kidney by using Pax8-Cre. The phenotypes of these mice include abnormal kidneys with reduced renal function, hypoplastic renal parenchyma with a thin cortex, missing of superficial layer of renal tubules, and absence of parietal epithelial cells in Bowman's capsule.⁶⁸ These results suggest an indispensable role of Wnt/ β -catenin signaling in the late stages of nephrogenesis, although one cannot completely exclude the possibility that some effects of β -catenin ablation may result from its role in regulating adherent junctions.

3.4 Wnt/PCP Pathway and Nephron Maturation

Increasing evidence suggests a critical role for Wnt/PCP signaling in kidney development and function. The PCP is defined for the cells in tissue perpendicular to the apical–basal axis, which was first described in *Drosophila*.⁶⁹ Deficiency of core PCP genes, such as *Vangl2*, *Celsr1*, *Fzd3/6*, and *Dvl1/2*, have been shown to disrupt asymmetric localization, convergent extension, hair cell organization, neural tube closure, and to cause cystic kidney in mammals.⁷⁰ Some PCP components are expressed in the renal developing epithelia, such as UB, RVs, and S-shaped body, suggesting their functions in cell division orientation, movements, adhesion, and contribution to morphogenesis of the mature nephron.⁷¹ Several systematic analyses have implicated the function of PCP in UB branching and elongation to determine tubular diameter, length, and shape.^{72,73}

Transgenic mouse models with mutations in Wnt ligands of the PCP pathway (*Wnt5a*, *Wnt7b*, *Wnt9b*, and *Wnt11*) exhibit UB branching defects. The noncanonical Wnt5a/Ror2 signaling in IM-derived nephric duct controls UB expansion, and *Wnt5a* knockout mice exhibit duplicated ureters and kidneys because of abnormal GDNF signaling and spatiotemporally aberrant interaction between MM and WD.^{46,47} The absence of Wnt7b ligand displayed normal development of cortical epithelium but was incapable of forming medullary zone and concentrated urine.⁵⁰ This phenotype is explained by the disorganization of cell division planes in the collecting duct epithelium of the emerging medullary zone. Likewise, Wnt9b is suggested to be essential in establishing the length and diameter of the

kidney tubules, while deletion of *Wnt9b* during kidney morphogenesis disrupts PCP in the epithelium and leads to polycystic kidney disease (PKD).⁵⁵ Besides its role in convergent extension in fish, Wnt11 regulates Ret/GDNF loop for UB branching and metanephric development.⁵⁷

The key PCP molecule *Vangl2* is expressed in UB, collecting duct, MM, and nephron, whose mutation impairs branching morphogenesis and causes cystic kidney.⁷⁴ After podocyte-specific ablation of *Vangl2* gene, the mutants show significantly smaller glomeruli with maturation defects.⁷⁵ These results indicate the important role of *Vangl2* in podocytes morphology and function.⁷⁵ Another *Drosophila* PCP protein, fat, is essential in vertebrate PCP pathway. Deletion of *fat4* caused cystic kidney owing to disrupted cell division and tubule elongation upon interaction with *Vangl2*.⁷⁶ The PCP component of *Daam1* is expressed at developing pronephric anlagen and interacts with the novel weak-similarity Rho-GEF (WGEF). Knockdown of *Daam1* led to downregulation of late pronephric epithelial markers, possible through *Daam1*/Rho-GEF axis to inhibit pronephric tubulogenesis.⁷⁷ Therefore, Wnt/PCP is fundamental for kidney development and function and requires to be the focus of more research.

3.5 Wnt Signaling and Cystogenesis

Wnt/ β -catenin signaling is involved in renal polycystic lesions, which was first illustrated by overexpression of β -catenin in epithelial cells of the kidney. The transgenic mice exhibited severe polycystic kidney with abnormal renal function, similar to human autosomal dominant polycystic kidney disease (ADPKD).⁷⁸ After conditional deletion of APC in renal epithelium, there is multiple cysts formation with increasing levels of β -catenin protein.⁷⁹ Aquaporin-1 (AQP1), the molecular marker of renal proximal tubules and thin descending limb of Henle, could interact with β -catenin in models of ADPKD. The *AQP1* knockout mice increased cysts development with upregulation of Wnt/ β -catenin signal.⁸⁰ These results show that the activation of Wnt/ β -catenin signaling is required for renal cystogenesis. Consistently, conditional stabilization of β -catenin with Hoxb7-Cre from mouse tubular epithelium led to cystic kidney and hydronephrosis.⁶⁶ On the other hand, the cystic kidney and abnormalities are also induced by loss of the Jouberin (Jbn) protein, owing to a downregulation of endogenous Wnt activity.⁸¹ Jbn was found to interact with and facilitate β -catenin nuclear accumulation, resulting in positive modulation of its downstream transcription.⁸¹ Our previous studies also demonstrate that global deletion of *LRP6* causes renal hypoplasia and cysts formation, further confirming the role of LRP6-mediated Wnt/ β -catenin signaling in the process.⁵⁹ However, there are controversies in the literature regarding the role of canonical Wnt/ β -catenin signaling in cystogenesis. Mice with *Inversin* gene mutation had developmental abnormalities and renal cysts formation, although canonical Wnt/ β -catenin signaling was not altered as defined in the Wnt reporter *BATlacZ* mice.⁸² Additional studies also indicate normal TCF/ β -catenin activity in two different models of PKD.⁸³ Therefore, the unique and precise regulation of Wnt/ β -catenin signaling is required during kidney development and disruption of which leads to a cystic abnormality in a content-dependent manner.

Polycystic kidneys are also caused by the genetic mutations, which are related to primary cilia and Wnt.⁸⁴ The impaired cilia led to a disturbed fluid flow and calcium influx that initiate cyst formation. Because the tubular epithelial cells undergo oriented cell division during tubular elongation, the Wnt/PCP signal might be critical for the cyst formation.⁸⁵ There is evidence that maturation of nephrons is associated with mitotic orientation and intrinsic PCP signal, and abnormality of this pathway causes polycystic kidney in animal models.⁸⁶ It is interesting to point out that gene mutation of cilia-associated protein *Inversin* led to nephronophthisis type II, which is an autosomal recessive cystic kidney disease with extensive renal cysts formation.⁸⁷ It becomes apparent that *Inversin* acts between canonical and noncanonical Wnt signaling for normal tubular differentiation.⁸⁷ Based on these observations, it is conceivable that Wnt/ β -catenin signaling is sufficient to induce cysts formation, but compromised Wnt/PCP pathway is also involved.⁸⁸ Therefore, both canonical and noncanonical Wnt signaling are important in kidney development, and disruption of either pathway can cause cystic kidney disease.⁸⁹ As many proteins, including Vangl, Fz, and Dvl, have been found to localize in the ciliary basal body,⁹⁰ changes in their expression and structure would eventually cause defective primary cilia in cystic kidney disease.

4. WNT SIGNALING AND KIDNEY DISEASES

4.1 Wnt Signaling in Acute Kidney Injury

Progresses have been made in recent years to demonstrate a key role of Wnt/ β -catenin signaling in kidney injury and fibrosis, which is summarized in several recent reviews (Table 2).^{6,13} In both acute kidney injury (AKI) and chronic kidney disease (CKD) animal models, Wnt/ β -catenin is activated, which could function as either renal protective or detrimental mechanisms.^{91,92} The AKI is described as a rapid decrease in kidney function, which involves hemodynamic alterations, inflammation, and endothelial and epithelial cell injury.⁹³ The outcome of AKI is either adaptive leading to the restoration of epithelial integrity or maladaptive progressing to CKD.⁹⁴ At different time points after AKI, the Wnt4-mediated β -catenin is activated, which contributes to recovery from renal injury. The activated β -catenin is able to promote cell cycle progression through its transcriptional targets, such as cyclin D1 in LLC-PK1 cells.⁹⁵ Using the *BATgal* and *Axin2-lacZ* Wnt signaling reporter mice, it has been shown that activation of Wnt7b signaling is renoprotective after ischemia reperfusion injury (IRI), and macrophages are the sources of Wnt7b during ischemic injury and repair process.⁹⁶ In vitro, β -catenin signaling reduces Bax-mediated apoptosis and improves cell survival after induction of metabolic stress in proximal tubular epithelial cells. Constitutively activated β -catenin also regulated Bax activation and translocation to mitochondria upon acute stress injury.⁹⁷ Consistent with these in vitro findings, mice with tubule-specific *β -catenin* knockout are more susceptible to AKI following either ischemic or toxic insults.⁹² These conditional knockout mice exhibit higher mortality rate and increased serum creatinine, and worsen the morphological injury. There is more tubular cell apoptosis in the β -catenin null kidneys exhibiting high levels of p53 and Bax.⁹² Another study using the Wnt agonist, a synthetic pyrimidine, also showed renal protective effects of Wnt signaling after IRI in rats through attenuating inflammation and oxidative stress, suggesting the potential pharmacological application of manipulating Wnt activity on preventing kidney injury.⁹⁸

Severe or repeated AKI will lead to incomplete renal recovery and often progresses to CKD. We have shown that mice subjected to 20 min IRI exhibit transient Wnt/ β -catenin activation, moderate AKI with complete recovery of renal function; whereas 30 min IRI causes sustained activation of this signaling and severe AKI, and eventually progresses to CKD characterized by renal fibrosis.⁹⁹ A sustained activation of Wnt/ β -catenin accelerates AKI to CKD progression characterized by interstitial myofibroblast activation and excessive extracellular matrix deposition, while blockade of Wnt/ β -catenin prevents AKI to CKD progression.⁹⁹ Therefore, the magnitude and duration of Wnt/ β -catenin activation plays a decisive role in determining the outcomes of AKI.^{6,100}

4.2 Wnt Signaling in Chronic Kidney Disease

Wnt/ β -catenin signaling is also activated in fibrotic kidney initiated by unilateral ureteral obstruction (UUO), as well as in many other models of CKD (Table 2).^{10,12,101,102} The regulation and actions of Wnt/ β -catenin signaling in the pathogenesis of fibrotic CKD has been reviewed previously.^{91,101} Secreted frizzled-related protein 4 (sFRP4), an endogenous extracellular Wnt antagonist, inhibits β -catenin activation and reduces renal fibrosis after UUO presumably via preventing Wnts binding to their receptors.¹² A systematic analysis for the Wnt ligands in mouse model of UUO revealed that 16 out of 19 different Wnts are induced in the kidney in different levels at some points during the injury.¹⁰ Notably, the cellular source of Wnt ligands in the fibrotic kidneys is largely from the tubular epithelium.^{103,104} The activation of Wnt signaling leads to dramatic accumulation of β -catenin and upregulation of its target genes, such as *c-Myc*, *Twist*, *TCF1*, and *fibronectin* in renal epithelial cells.¹⁰ Both in vitro and in vivo studies illustrate that Wnt/ β -catenin controls several key fibrosis-related downstream genes, such as *Snail1*, *fibronectin*, *plasminogen activator inhibitor-1 (PAI-1)*, *matrix metalloproteinase 7 (MMP-7)*, and multiple components of the renin–angiotensin system (RAS), including *angiotensinogen*, *renin*, *angiotensin converting enzyme (ACE)*, and *angiotensin receptor type 1 (AT1)*.^{11,105–108} Targeted inhibition of Wnt/ β -catenin signaling by ICG-001, a small molecule peptidomimetic that selectively inhibits β -catenin signaling in a CBP-dependent fashion,^{109,110} suppresses matrix expression and ameliorates renal interstitial fibrosis.¹¹¹ Therefore, inhibition of Wnt/ β -catenin signaling may be an effective strategy to ameliorate kidney injury and fibrotic lesions in various models of CKD.⁹¹

The role of Wnt/ β -catenin in renal fibrogenesis is supported by using the soluble form of Klotho as a secreted Wnt antagonist in renal fibrotic models. Klotho is antiaging protein that is highly expressed in renal tubular epithelium of normal kidney, which is suppressed in the elderly and in patients with CKD.^{112,113} Klotho is present as full-length, transmembrane protein or secreted, soluble form. Both membranous and soluble forms of Klotho can bind with multiple Wnt ligands and represses their target genes transcription.¹¹⁴ Overexpression of Klotho clearly hampers the activation of Wnt signal in mice with UUO, accompanied by reducing extracellular matrix deposition, bypassing the G2/M arrest and diminishing fibrotic cytokine production.^{114,115} TGF- β 1, a master regulator of tissue fibrosis, could suppress Klotho expression and concomitantly activates β -catenin to promote myofibroblast activation and renal fibrosis.¹¹⁴ Klotho also attenuates Wnt1-triggered activation of RAS in

a dose-dependent manner in renal epithelial cells.¹¹⁶ It is concluded that Klotho protects against renal fibrosis through sequestering and antagonizing Wnt/ β -catenin signaling.

4.3 Wnt Signaling in Podocytopathy and Proteinuria

Activation of Wnt/ β -catenin signaling also play a crucial role in mediating podocyte dysfunction, proteinuria, and glomerulosclerosis, leading to end stage renal disease (ESRD).¹³ Glomerular β -catenin is activated in adriamycin-induced kidney injury characterized by podocyte damage and albuminuria. In contrast, podocyte-specific β -catenin knockout mice are protected against albuminuria after adriamycin treatment.^{11,117} These results confirm a critical role for Wnt/ β -catenin signaling in the development of podocytopathy and proteinuria. Further studies using the same conditional knockout mice show that β -catenin is instrumental in disrupting podocyte slit diaphragm (SD), leading to an impaired glomerular filtration barrier.^{117,118} Studies also demonstrated that Wnt/ β -catenin plays a role in mediating the transforming growth factor- β 1 (TGF- β 1)-induced podocyte injury and proteinuria in vitro and in vivo.¹¹⁹ Overexpression of Wnt antagonist *Dkk-1* gene alleviates TGF- β 1-triggered podocyte damage and albuminuria. The action of β -catenin on podocytes includes its role in triggering ubiquitin-mediated degradation of Wilms' tumor 1 (WT1), a key podocyte-specific transcription factor that is critical to maintain podocyte integrity and function.¹²⁰ In that regard, β -catenin specifically targets WT1 for protein degradation, finally leading to podocyte dedifferentiation and mesenchymal transformation.¹²⁰

Given the importance of β -catenin activation in mediating podocyte injury, it is conceivable that strategies modulating its activity may be effective in ameliorating podocytopathy and proteinuria. Indeed, vitamin D analogs, such as paricalcitol, preserves podocyte integrity and function, inhibits proinflammatory cytokines, suppresses expression of the fibrogenic genes, and also ameliorates established proteinuria in mice after adriamycin injection.¹²¹ Studies also indicate that angiotensin II (Ang II), the principal effector of RAS activation, acts at upstream of Wnt/ β -catenin signaling, impairs podocyte integrity and causes albuminuria in mice.¹²² The Wnt antagonist *Dkk1* attenuates Ang II-induced podocyte injury in vitro and in vivo.¹²² In addition, high glucose is shown to impair podocyte integrity by suppressing *podocin* and *nephrin* and inducing (*pro*)*reninreceptor* (*PRR*), *Wnt3a*, β -catenin, and *Snail1*. These results suggest a potential role of PRR-Wnt/ β -catenin-Snail1 pathway in high glucose-triggered podocyte injury.¹²³ More interestingly, all RAS genes, including *angiotensinogen*, *renin*, *PRR*, *ACE*, and *AT1* are found to be novel downstream targets of Wnt/ β -catenin, as overexpressions of either β -catenin or different Wnt ligands induces, but β -catenin inhibitor ICG-001 inhibits, their expression.^{15,108,124} Thus, there might be a vicious cycle between Wnt/ β -catenin and RAS in the process of podocyte injury, and disruption of this cycle formation will preserve podocyte function and prevent proteinuria.¹³

4.4 Wnt Signaling and Human Kidney Disease

Aside from its roles in cultured cells and animal models, Wnt/ β -catenin is also activated in clinical human samples of CKD.¹⁰³ Active β -catenin is detectable in the podocytes of human kidney biopsy of CKD, such as diabetic nephropathy (DN) and focal segmental glomerulosclerosis (FSGS).¹¹ Increased nuclear β -catenin accumulation is discovered in the peripheral blood leukocytes from immunoglobulin A nephropathy (IgAN) patients,

suggesting that a hyperactivation of Wnt signal might contribute to the pathogenesis of IgAN.¹²⁵ Upregulation of Wnt/ β -catenin components is documented in the glomeruli and podocytes of diabetic kidney disease (DKD) patients, who exhibit glomerular basement membrane (GBM) abnormalities and albuminuria.¹¹⁸ There is increased activation of Wnt signaling in human collapsing glomerulopathies, indicating a potential role of Wnt pathway in the regulation of mature podocytes cell cycle progression and proliferation in renal disease state.¹²⁶ In lupus nephritis patients, active Wnt/ β -catenin signal is accompanied by increasing levels of plasmatic Dkk-1,¹²⁷ probably reflecting that Dkk1 is a target of the β -catenin signaling.¹²⁸ These alterations suggest a close relationship between hyperactive Wnt signaling and the pathogenesis of lupus nephritis.¹²⁷ Collectively, the activation of Wnt signaling in AKI and CKD after injury triggers adaptive or maladaptive responses depending on the injury severity and duration. This activation could be indispensable for kidney repair and regeneration, or promotes disease progression and fibrosis in humans as well.^{6,100}

4.5 Wnt Signaling and Kidney Cancer

As there are similarities between embryonic growth and abnormal cell proliferation in cancer, the Wnt signaling molecules are considered as candidates for the development of kidney cancers. The renal cell carcinoma (RCC) is the major form of kidney tumor with high frequency. Studies showed that Wnt1 is upregulated and associated with increased tumor size, more advanced stage and invasiveness in clear cell RCC (ccRCC).¹²⁹ After screening normal kidney and RCC cell lines and tissues, investigators found that Wnt10a is significantly induced and acts as an independent risk factor for RCC carcinogenesis and progression.¹³⁰ However, *Wnt7a* gene is inactivated in ccRCC and exhibits tumor suppressor properties, and there is positive correlation between tumor stage and *Wnt7a* hypermethylation.¹³¹ These observations demonstrate unique differences for canonical Wnts (Wnt1, Wnt10a) and noncanonical Wnts (Wnt7a) during tumorigenesis. The mRNA levels of Wnt receptors *Fzd5* and *Fzd8* are increased in RCC accompanied by active β -catenin signal and high levels of Wnt target cyclin D1, so *Fzd5* and *Fzd8* are considered as biomarkers in RCC.¹³² Another receptor, *Fzd7*, also shows higher levels of expression compared with surrounding normal tissues in RCC, which might be activated by a Wnt3a-mediated pathway.¹³³ Altered expression of β -catenin is also detected in RCC, and abnormal accumulation of β -catenin, at least partially, contributes to renal carcinogenesis.¹²⁹ Overall, Wnt signaling is constitutively activated in RCC and functional loss of Wnt antagonists may be one of the reasons for that process, and could be candidate for targeted therapies.¹³⁴ Additional evidences showed that Wnt signal not only participates in RCC, but also in the pathogenesis of embryonic kidney-derived tumor, Wilms' tumor (WT) or nephroblastoma, one of the most common pediatric malignancies.¹³⁵ Because Wnt4 serves as critical renal developmental factor, the mutations of its downstream *β -catenin* gene might cause WTs. A protein named WTX, which is mutant and encoded by Wilms' tumor gene in the X chromosome, could form a complex with β -catenin to promote its ubiquitination and degradation.¹³⁶ Thus, both RCC and WTs require β -catenin signal participation for the process of tumorigenesis.

5. CONCLUSIONS

Normal kidney development requires complex and precise cell-cell communications, in which Wnt signaling is one of the main mediators. Extensive studies in last decades have revealed that Wnt signaling is indispensable not only in normal nephrogenesis but also in kidney repair and regeneration after AKI, as well as in the evolution of various CKD characterized by tissue fibrosis and renal insufficiency. Both canonical and noncanonical Wnt signaling are instrumental for UB induction, nephron formation, and maturation. Dysregulation of Wnt signaling is implicated in a wide variety of kidney disorders ranging from fibrosis, cystic formation, proteinuria to tumorigenesis. There is a tremendous progress in the field during last several years through the discovery of novel targets of Wnt/ β -catenin signaling and delineating new mechanisms of its action. As there are many Wnt antagonists, such as small molecule inhibitor ICG-001 and soluble Klotho are currently available, it is hopeful that manipulation of this signaling pathway by diverse strategies will eventually translate into effective therapies for patients with various kidney disorders.

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Fig. 1.

Different Wnt signaling pathways. (A) Canonical Wnt/β-catenin signal pathway. When the signal is in “ON” state, Wnt ligands bind to Frizzled (Fzd) receptors and LRP5/6 coreceptors, which causes Dishevelled (Dvl) to inhibit the β-catenin destruction complex consisting of adenomatous polyposis coli (APC), Axin, and GSK-3β. Pro(reinin) receptor (PRR) is also an obligatory component of the Wnt receptor complex and required for canonical Wnt/β-catenin signaling. Stabilized β-catenin is able to enter the nucleus and acts with T cell factor (TCF)/lymphoid enhancer-binding factor (LEF) transcription factor for specific gene expression. When the signal is “OFF,” Dvl cannot act on the destruction

complex and β -catenin is then phosphorylated by GSK-3 β , leading phosphorylated β -catenin for degradation by ubiquitin (Ub)-proteasome system. (B) Noncanonical Wnt/PCP signal pathway. In Wnt/PCP pathway, Wnt ligands can bind Fzd, Vangl2, and PTK7, then acts with Rho/Rac1 small GTPases and JNK kinases through Dvl. Subsequently, cytoskeleton organization and cell migration are regulated in response to the signal. Daam1 acts with Dvl for downstream effectors, while Prickle inhibits this function. (C) Noncanonical Wnt/Ca²⁺ pathway. Wnt ligand binding activates Fzd/Dvl and induces a rise in intracellular Ca²⁺ levels. Elevated intracellular Ca²⁺ activates calcium calmodulin-dependent protein kinase II (CaMKII), calcinurin (CaN), and protein kinase C (PKC), which activate nuclear transcription factors (NFAT and NF- κ B) and promote the expression of downstream target genes.

Fig. 2.

Diagram depicts the major events in mammalian nephrogenesis. There are three stages of kidney development in a temporal sequence: pronephros, mesonephros, and metanephros. The pronephros develops at embryonic day 8.5 (E8.5) in mice. The mesonephros develops by the formation of mesonephric tubules from the intermediate mesoderm. The metanephros, begins at E10.5 in mice, finally becomes the permanent and functional kidney in mammals. *MM*, Metanephric mesenchyme; *ND*, nephric duct; *UB*, ureteric bud; *WD*, Wolffian ducts.

Fig. 3.

Wnt/β-catenin signaling is activated during kidney development. (A) Diagram depicts the construction of the Wnt/β-catenin responsive reporter TOPgal mice. (B–E) Wnt/β-catenin is activated in different time points during kidney development. The *black lines* in Panels B and C indicate dissection planes for corresponding embryonic kidneys of Panels D and E, respectively. At E10.5 (D) and E12.5 (E), Wnt/β-catenin signaling reporter TOPgal is activated in the nephric tube (NT), Wolffian ducts (WD), and metanephric mesenchyme (MM). (F–G) GSK-3β inhibition by lithium chloride leads to β-catenin-mediated gene expression in TOPgal reporter mice. Maternal injection of the Wnt agonist LiCl significantly enhanced the activity of the reporter β-galactosidase (G), compared with the NaCl-treated mouse embryonic kidneys (F). *LEF*, Lymphoid enhancer-binding factor; *TCF*, T cell factor; *UB*, ureteric bud.

Table 1

Wnt Components Involved in Kidney Development.

Wnt Components	Developmental Roles	KO Renal Defects	References
Wnt1	Inducing tubulogenesis	?	34
Wnt2b	Inducing ureter branching	?	37
Wnt4	Initiating renal development	Müller duct regression and renal dysgenesis	38–44
Wnt5a	Regulating metanephric mesenchyme	CAKUT	45–48
Wnt6	Inducing ureter bud branching	?	49
Wnt7b	Maintaining cortico-medullary axis	Fails to form medullary zone and concentrate urine	50
Wnt9b	Regulating progenitors in metanephric mesenchyme	Disrupts tubular cell division and increases diameter	51–55
Wnt11	Autocrine factor in nephric duct and ureteric epithelium	Disrupts UB branching and causes renal hypoplasia	56–58
Lrp6	Acting through Ret signal pathway for renal defects	Hypoplasia cystic kidney	59
Frizzled4	Coordinating with Frizzled8	Frizzled4/8 double KO exhibits reduced ureteric bud growth	61
Frizzled8	Coordinating with Frizzled4 to maintain normal ureteric epithelial function	Frizzled4/8 double KO exhibits reduced ureteric bud growth	60
GSK-3β	Inducing early nephrogenesis	?	62,63
β-Catenin	Critical for nephron progenitor maintenance and nephrogenesis	Conditional deletion at different lineages causes various renal defects, including aplasia, hypoplasia and cysts	64–68
Vangl2	Indispensable for normal morphogenesis of both UB and MM-derived structures	Impairs branching morphogenesis and causes cystic kidney	73
Fat4	Regulating cell division and tubular elongation via acting with vangl2	Cystic kidney	75
Daam1	Promoting pronephric tubulogenesis	Disrupts tubule elaboration and branching in pronephic proximal segments	76

CAKUT, Congenital anomalies of the kidney and urinary tract; MM, metanephric mesenchyme; UB, ureteric bud; ?, undefined.

Table 2

Wnt Components and Kidney Diseases.

Diseases	Wnt Components	Roles	References
AKI	Wnt4	Promotes tubular cell cycle progression	94
	Wnt7b	Protective effects after IRI	95
	Wnt agonist	Improves renal function after IRI	97
	Tubular β -catenin	Protects against ischemic and toxic AKI	96–98
CKD	Wnt ligands	Increased renal expressions after UUO	10,102,103
	Wnt1	Tubular induction of Wnt1 causes renal fibrosis	103
	Dkk1	Inhibition of renal fibrosis after UUO	10
	sFRP4	Inhibition of renal fibrosis	12
	Wntless	Tubular KO reduces renal fibrosis after UUO	102
	Klotho	Sequesters Wnts and inhibits kidney fibrosis	113,114
	Fibroblast β -Catenin	Activation of β -catenin in interstitial pericytes/fibroblasts causes renal fibrosis	101
	Tubular β -catenin	Tubular deletion of β -catenin fails to affect renal fibrosis after UUO	135
	PRR	Amplifies Wnt/ β -catenin signaling and aggravates renal fibrosis	15
	Podocytopeny	Wnt1 overexpression induces podocyte injury and albuminuria	11
Cancer	β -Catenin	Podocyte-specific deletion of β -catenin reduces proteinuria	11,13,115,118
	β -Catenin	Podocyte-specific stabilization of β -catenin causes podocytopeny	116
	Wnt1	Positively correlates with tumor progression in RCC	127
	Wnt7a	Tumor suppressor properties in RCC	129
	Wnt10a	Independent risk factors for RCC carcinogenesis	128
	Fzd5, Fzd8	Biomarkers in RCC	130
	Fzd7	High expression in RCC	131
	β -Catenin	Abnormal accumulation in RCC carcinogenesis, mutation involved in WTs	127

AKI, acute kidney injury; CKD, chronic kidney disease; IRI, ischemia reperfusion injury; PRR, pro(renin) receptor; RCC, renal cell carcinoma; UUO, unilateral ureteral obstruction.