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Review Article

Planar Cell Polarity Pathway in Kidney Development and Function

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The evolutionarily conserved planar cell polarity (PCP) signaling pathway controls tissue polarity within the plane orthogonal to the apical-basal axis. PCP was originally discovered in *Drosophila melanogaster* where it is required for the establishment of a uniform pattern of cell structures and appendages. In vertebrates, including mammals, the PCP pathway has been adapted to control various morphogenetic processes that are critical for tissue and organ development. These include convergent extension (crucial for neural tube closure and cochlear duct development) and oriented cell division (needed for tubular elongation), ciliary tilting that enables directional fluid flow, and other processes. Recently, strong evidence has emerged to implicate the PCP pathway in vertebrate kidney development. In this review, we will describe the experimental data revealing the role of PCP signaling in nephrogenesis and kidney disease.

1. General Introduction

Development of the mammalian kidney is a complex process involving repeated local interactions between progenitor cells of the intermediate mesoderm and branches of the ureteric bud that culminate in the formation of thousands (mouse) or hundreds of thousands (humans) of nephrons (extensively reviewed in [1, 2]). Each nephron consists of phenotypically and functionally distinct segments; an ultrafiltrate of plasma generated by the glomerulus is delivered to the proximal tubule followed by the loop of Henle and distal convoluted tubule, fused to a collecting system derived from the arborized ureteric bud. As it passes along the nephron, tubular fluid is modified by reabsorption of water, key electrolytes, and nutrients while unwanted metabolic waste products are allowed to flow into the collecting system and out to the bladder. Nephrogenesis relies on a differentiation cascade that requires timely changes in cell shape, movement, and alignment that lead to clusters of specialized epithelia lining each segment. Disturbance of these molecular and cellular events manifests in a wide variety of congenital anomalies of kidney and urinary tract in humans [3]. In the past 20–30 years, a great deal has been learned about the physiology of each nephron segment but the molecular events that specify cell fate and align cells along the nephron are poorly understood.

During embryogenesis, the mechanisms that establish cellular polarity are critical for complex organs such as the kidney. Polarization within cells can be thought of as a cell's sense of direction. Apical-basal (AB) polarity is the most thoroughly studied axis of cell polarity. Experiments in *Drosophila* revealed that the AB polarity is initially established by reciprocal interactions between three polarity complexes: apical Crumbs and Par complexes with the basal Scribble complex [4–7]. Once appropriate apical and basal membrane domains are established, effector molecules linked to these polarity complexes organize the actin cytoskeleton and vesicular protein transport in a spatially polarized manner. The mechanisms controlling vertebrate AB polarity are not yet well-defined but a complex network of fruit fly AB-related proteins has been identified which is critical for generation and maintenance of epithelial cell polarity in vertebrates [8, 9]. Overall, AB polarity is crucial for tissue barrier formation, vectorial transport functions, cell adhesion, cytokinesis, and other cellular events, which are indispensable for the morphogenesis and functions of epithelial tissues.

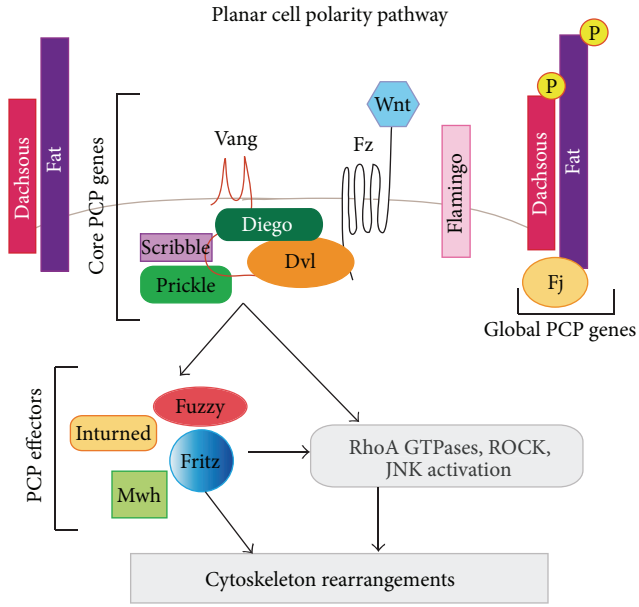

Figure 1: *The PCP signaling pathway in Drosophila*. The PCP pathway is activated when a Wnt ligand binds to a Frizzled (Fz) receptor and induces a clustering of the core PCP proteins to either proximal (Van Gogh-like (Vangl) and Prickle (Pk)) or distal (Dishevelled (Dvl) and Fz, Diego) cellular domains. Activation of PCP signaling is associated with Dvl phosphorylation. Flamingo (Celsr) is found at both sides. Apical-basal regulator Scribble also regulates PCP in the fruitflies and genetically interacts with Vangl2. Dachsous (Ds) and Fat (Ft) protocadherins form heterotypic complexes at both sides of the cell and provide global positioning cues; phosphorylation of Ft and Ds by the Four-jointed (Fj) kinase regulates the strength of the Ds-Ft complex. Asymmetric distribution of the core PCP proteins induces asymmetric clustering and activation of downstream PCP effectors Inturned (In), Fuzzy (Fuz), Fritz, and multiple wing hair (Mwh) as well as a Rho GTPase, Jun kinase, and others. This leads to actin rearrangement necessary for polarized asymmetric distribution of cellular appendages.

In addition to AB polarity, many epithelial tissues display a second axis of polarity along an orthogonal "proximal-distal axis," known as planar cell polarity (PCP) (reviewed in [10, 11]). In the case of the renal tubule, this would be cell polarity along the path of tubular flow. PCP is observed in both invertebrates, for example, as a uniform orientation of hair on fruit fly wing cells (where it was initially described and studied) [12–14] and vertebrates (e.g., as a uniform orientation of scale on fish) [10]. These patterns are orchestrated by an evolutionarily conserved PCP signaling pathway (Figure 1). In mammals, mutations of PCP pathway components lead to multiple developmental abnormalities including neural tube and cardiac defects and misorientation of hair cells in the cochlea, lung, limb, facial anomalies, and other defects (reviewed in [10]). These congenital abnormalities underscore the critical role for the PCP pathway in organogenesis. A role for PCP genes in nephrogenesis has recently been proposed (reviewed in [15, 16]). In this review, we provide an update on current understanding of how the PCP pathway contributes to kidney development and maintenance of adult renal function. We then discuss how disturbances of the PCP pathway contribute to human kidney disease.

2. Mammalian Kidney Development

Mammalian kidneys are derived from the mesodermal germ layer. In mice and humans, a portion of the intermediate mesoderm on either side of the spine is transformed into an epithelial structure, the nephric duct (ND), which extends caudally as a single tube. Development of a permanent "metanephric" kidney in mammals starts at the 5th week of gestation in humans and approximately at day 10.5 of embryonic development (E10.5) in mice when the ureteric bud (UB) grows out from the posterior portion of the ND and invades the metanephric mesenchyme (MM), a column of undifferentiated nephron progenitor cells situated laterally to the posterior ND [1]. Signals from the MM induce repetitive branching of the UB that generates the entire renal collecting system (collecting duct tree, renal pelvis, and ureter) (Figure 2(a)). Cellular events implicated in UB branching include cell migration, oriented cell division, and cytoskeletal rearrangements [17]. Concomitantly, signaling molecules secreted by the UB cause the MM to condense around the UB tips and form organized structures: renal vesicles and comma- and S-shaped bodies that represent successive stages of nephrogenesis [17]. In response to inductive UB signals, nephron progenitor cells around the UB tip (cap mesenchyme) undergo a mesenchyme-to-epithelium transition involving changes in cell adhesion properties and cell polarization along the apical-basal and proximal-distal axes. In mice, the ureteric bud continues to arborize and induce new generations of nephrons into the postnatal period. By postnatal day 14 (P14) nephrogenesis comes to an end and the final complement of ~13,000 nephrons is fixed for life. In humans, nephrogenesis ends by 38 weeks gestation, yielding a final complement of about 800,000 nephrons/kidney [1].

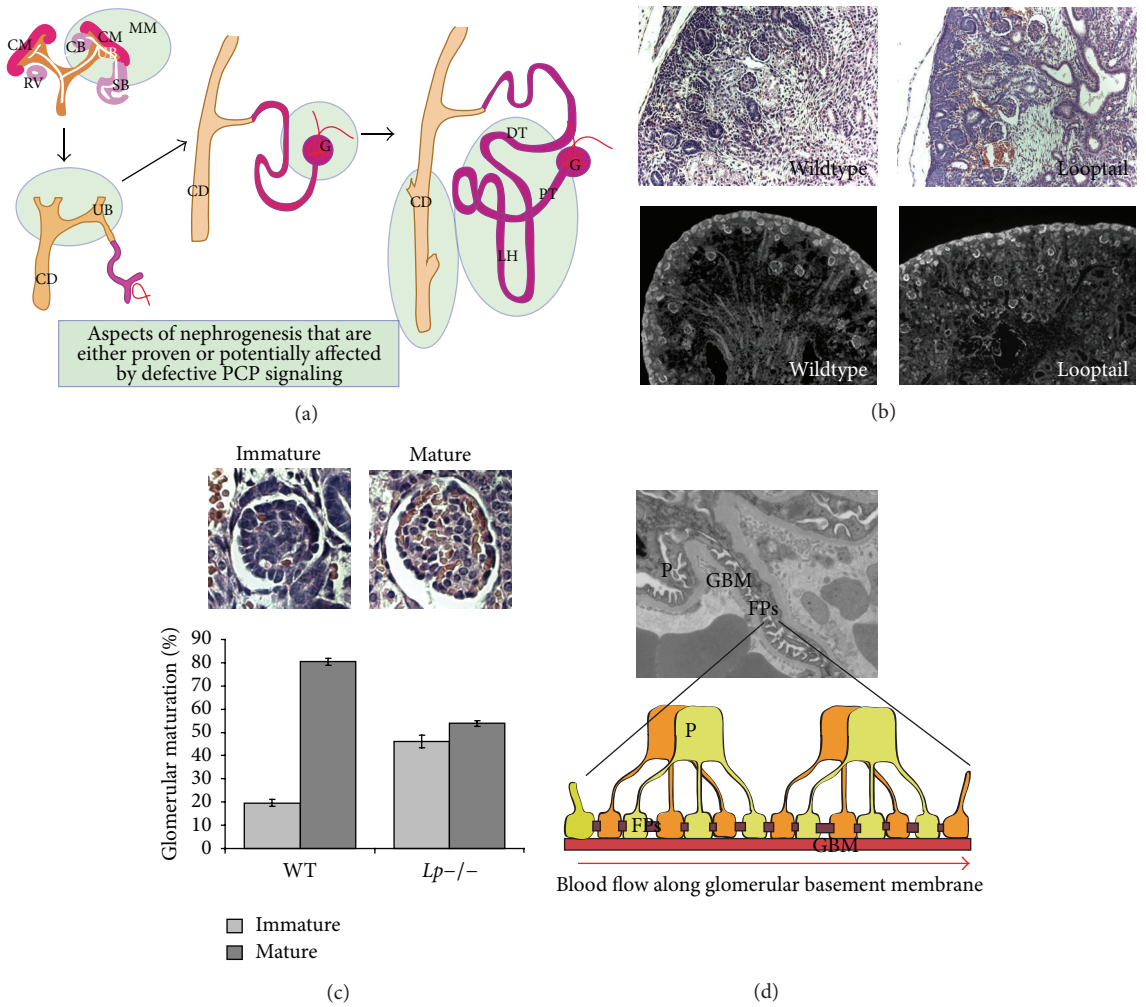

Figure 2: *Normal kidney morphogenesis and kidney defects in Looptail mouse*. (a) Stages of kidney development: ureteric bud (UB) invades the metanephric mesenchyme (MM) to induce clustering of the nephron progenitor cells above UB tip (cap mesenchyme, CM) to epithelize sequentially into a renal vesicle (RV), comma-shaped body (CB), and S-shaped body (SB). The SB fuses with an arborizing collecting duct (CD) at the distal end and forms a glomerulus (G) at the proximal end. The SB elongates and differentiates to form proximal tubules (PT), loop of Henle (LH), and distal tubules (DT). The shaded areas designate morphogenetic processes where the PCP pathway may be involved. (b) *Upper panels*: hematoxylin and eosin-stained E17.5 wildtype (*left*) and *Looptail* (*right*) kidneys, magnification ×200; *lower panels*: WT1 antibody-immunostained wildtype (*left*) and *Lp* (*right*) kidney images, magnification ×100. (c) *Upper panels*: images of immature (capillary-loop stage) and more mature glomeruli; *lower panel*: statistical analysis of glomerular developmental delay in *Lp* versus wildtype kidneys. (d) Electron microscopy of mouse glomerulus (*left*) and a schematic depiction of the podocyte foot processes along GBM (*right*): podocyte (P), glomerular basement membrane (GBM), and foot processes (FPs). The results of (b) and (c) were partially published in Rocque, 2014, JASN and are published with the permission of JASN.

A complex system of transcription factors and signaling molecules govern UB branching, induction of nephron progenitor cells, the mesenchyme-to-epithelium transition (MET), and terminal differentiation of specific nephron segment cells (excellently reviewed by Costantini [17]). A set of transcription factors (e.g., Six2 and Osr1) define cap mesenchyme-derived progenitor cells which give rise to the majority of nephron segments [18, 19]. Action of the Wnt/β-catenin pathway is crucial for the survival and self-renewal of nephron progenitor cells, MET induction, and UB branching [20–22]. The transcription factor PAX2 is a key regulator of early kidney development. Its loss results in renal agenesis due to failure of ND development and UB outgrowth [23]. Of particular importance to UB arborization are interactions between the receptor tyrosine kinase, Ret, and glial glycophosphatidylinositol-linked coreceptor, GFRα1, with the glial derived neurotrophic factor, GDNF [17]. Mutations of any of these three genes result in renal agenesis [24–26]. Mutations of transcription factor genes that regulate expression of GDNF (e.g., Eya1 or Hox11) or Ret (e.g., Gata3) also cause renal agenesis or hypoplasia [27–29]. In general, failure of any of the early nephrogenic processes manifests in renal anomalies ranging from complete renal agenesis to modest renal hypoplasia/dysplasia with associated ureteral defects, conditions known in humans as Congenital Anomalies of Kidney and Urinary Tract, CAKUT [3].

Upon formation of the nephron epithelium, further specification is required to give rise to the specific nephron segments [30, 31]. For example, Notch/γ-secretase signaling is necessary for development of the proximal tubular and glomerular segments [32–34]. Loss of Notch2 in the MM leads to loss of proximal cell types without affecting the distal nephron epithelium or UB branching [35]. Podocyte precursors are specified at the most proximal part of the S-shaped body and this process relies on the interplay between Pax2 and Wilms-Tumor 1, WT1, genes [36, 37]: initially, Pax2 induces high levels of WT1 expression needed for podocyte specification [38], yet suppression of Pax2 expression by WT1 is later required to complete podocyte differentiation [39, 40]. Once podocyte precursors are specified, they undergo extensive metamorphosis (discussed in detail in Section 4.2) [41]. Recently, strong evidence has implicated the planar cell polarity pathway in some aspects of kidney development. These issues are discussed in the sections below.

3. Planar Cell Polarity Pathway

3.1. PCP Functions in Drosophila. 40 years ago, Lawrence and Shelton described a uniform ommatidial pattern in the retina of the milkweed bug, *Oncopeltus fasciatus*, and hypothesized that it might be regulated by an unknown gradient factor(s) [42]. In 1982, Gubb and Garcia-Bellido described planar polarization of hairs on the wing cells of the fruit fly, *Drosophila melanogaster,* and identified several genetic loci responsible for specific planar arrangements of wing hairs [12]. These pioneering works initiated a new field of research into planar cell polarity (PCP). In *Drosophila*, many organs display uniform orientation of cellular structures or appendages within the tissue: for example, each cell in the fly wing produces a single hair at the most distal point of the cell (indicative of polarity within an individual cell); all hairs are distally oriented (indicating a global tissue polarity); in the multifaceted *Drosophila* eye, each of the ~800 ommatidia is oriented in relation to the eye's midline (reviewed in [10]). This planar polarity pattern relies on PCP genes. There are two main classes of PCP genes. The first includes atypical protocadherins, Fat (Ft) and Dachsous (Ds), and the Golgi-associated kinase Four-jointed (Fj). Ft and Ds are expressed on both sides of each wing cell and form heterodimers which may act as bridges between the two adjacent cells. Ft is equally distributed along the wing blade but expression of Ds and Fj is inversely graded along the tissue: high Ds is expressed at the proximal margin while Fj accumulates at the distal zone of the wing [43]. The binding affinities between Ft and Ds are regulated by Fj, which phosphorylates both cadherins. As a result, the Ft-Ds complex expression is graded along the tissue and this provides a global polarity cue [44, 45]. The second class of PCP molecules are encoded by "core" PCP genes: the WNT receptor Frizzled (Fz), transmembrane proteins Van Gogh/Strabismus (Vang/Stbm), and Flamingo/Starry Night (Fmi/Stan) and cytoplasmic proteins Dishevelled (Dsh/Dvl), Prickle (Pk), and Diego (Dg) [46, 47] (Figure 1). Core PCP proteins define the axis of planar polarization in each cell and are sensitive to long-range input from upstream polarity cues [48]. Mutations of the core genes result in PCP defects in all fruit fly tissues studied [10]. In addition to global and core PCP proteins, several planar polarity effector proteins have also been identified including Inturned (In), Fuzzy (Fy), Fritz (Frtz), and multiple wing hair (Mwh). In, Fy, and Frtz act as a discrete genetic and biochemical module to regulate position and number of hair on each wing cell [49]. The apical-basal regulator Scribble (Scrib) interacts genetically and biochemically with Vang/Stbm, Scrb functions as Vang effector exacerbating Vang ommatidia and wing hair planar polarity defects [50]. In some tissues, the proteins of the RhoA family of small GTPases (Rho1 and Rac1) serve as effectors to regulate actin rearrangements [51–53]. The RhoA regulatory Drosophila Rho-associated kinase (Drok) also acts as a PCP effector: it affects Myosin II and actin cytoskeletal rear rangements [54]. Jun-Kinase (JNK) is activated by PCP signaling to mediate maturation of cytoskeleton dynamics [52, 53, 55, 56]. Unlike core PCP genes (needed for PCP in all tissues), specific effector genes are required for the planar polarity in a restricted subset of tissues.

Planar cell polarity is achieved via the asymmetric localization of core PCP protein complexes. Earlier papers suggested that the Ft-Ds-Fj module establishes an axis of polarity across the tissue and this triggers the asymmetric distribution of core PCP molecules in each individual cell [57]. However, this upstream-downstream relationship between the global and core PCP modules has been questioned and alternative model has been proposed in which the two cassettes function in parallel with some cross talk between them [58, 59]. Recently, Wu et al. showed that an early instructive PCP signal is provided by the two *Drosophila* Wnt members, Wingless (Wg) and Wnt4, which are expressed in a gradient and act redundantly as Fz ligands [48]. Wg/Wnt4 -Fz binding regulates Fz activity, which, in turn, provides the planar directional cue and triggers asymmetric relocalization of PCP protein complexes. In the fly wing epithelium, Vang forms a complex with Pk at the proximal domain of the cell; the Vang/Pk complex excludes the Fz/Dvl complex which demarcates the distal domain of the same cell [60–64]. The asymmetry is sustained by inter- and intracellular mechanisms that collectively generate a negative feedback loop that enhances and sustains asymmetric PCP protein distribution [61, 65, 66]. Wu et al. showed that Fz (which is localized at the distal part of one cell) binds to an extracellular loop of Vang localized at the proximal side of a neighboring cell; stability of the Fz-Vang intercellular interaction depends on Wg/Wnt4 concentration [48]. The Fz-Vang extracellular binding leads to stabilization of both Vang/Pk and Fz/Dvl complexes to the opposite cellular domains [66]. Intracellularly, Pk is degraded by the Smurf ubiquitin ligases at the distal side, whereas, in the complex with Vang, stabilized Pk precludes accumulation of Dvl in the proximal domain [67]. Asymmetry of the core PCP proteins further translates into the asymmetric localization of PCP effectors: for example, the In-Fy-Frtz cassette is detected at the proximal edge of wing cells and controls the distal accumulation of Mwh (a formin-homology containing protein); the latter directly regulates initiation of actin polymerization at the most distal aspect of the wing cell [68].

Recently, Classen et al. demonstrated that, in addition to controlling actin rearrangements, PCP signaling was necessary for normal hexagonal packaging of wing cells [69]. In order to achieve hexagonal shape, cells must remodel their intercellular junctions. This process is modulated by PCP-mediated endocytosis of E-Cadherin [69]. PCP signaling also regulates E-cadherin turnover and junctional levels during tracheal morphogenesis and this, in turn, promotes cell intercalation and tracheal elongation [70]. Taken together, PCP molecules control several critical cellular processes during fly development, underscoring the general importance of PCP signaling to *Drosophila* morphogenesis.

3.2. PCP Functions in Vertebrates. Homologs of the *Drosophila* PCP genes operate in vertebrates [10]. Various Wnt ligands (Wnt5a, Wnt9b, and Wnt11) activate PCP signaling in vertebrates [71–74]. Because Wnt, Frizzled, and Dishevelled molecules are involved (all are the key regulators of the canonical Wnt/β-catenin pathway), PCP signaling has historically been also referred to as a "noncanonical" Wnt signaling pathway. Vertebrate genomes contain two vertebrate Vang genes, Van Gogh-like (Vangl) 1 and Vangl2 [75], three Fmi homologous (Celsr1-3), three Dsh homologous genes, Dvl1–3, four vertebrate homologs of Pk, Pk1-4, four homologs of Ft gene, Fat1-4, and two Ds genes, Dachsous1 and Dachsous2. There are single Fuzzy, In, and Fritz vertebrate genes [76–78]. The AB regulator Scribble 1 was implicated in murine PCP [79], and the atypical tyrosine kinase Ptk7 was also shown to regulate mammalian PCP [80]. In mice, the PCP pathway controls the uniform orientation of stereocilia bundles on cochlear hair cells [81] and patterning of hair on the head [82], characteristics reminiscent of hair alignment on fruit fly wings. Additionally, in vertebrates, the PCP pathway has been adapted to morphogenetic processes such as neural tube closure [75, 79, 80, 83, 84], development of the cardiac outflow tract [83, 85–87], face and palate structure [88], somite organization [89], lung branching morphogenesis [90], cochlear development [81, 91, 92], and other morphogenetic processes.

The prototypic feature of many mouse PCP gene mutants is a severe neural tube defect, *craniorachischisis*, which represents complete failure of neural tube closure (extensively reviewed in [93, 94]). Neural tube formation is a complex process which begins with flattening of the neural plate. Subsequent shaping then depends on the morphogenetic process of convergent extension, CE [95, 96]. CE was first described in developing *Xenopus laevis* embryos during gastrulation and is a general term for a process whereby cells intercalate to decrease the width of a structure in one direction (convergence) and to increase the length of the structure in the perpendicular axis (extension) [97]. Sokol showed that overexpression of the *Xenopus* Dvl2 mutant Xdd1 causes neural tube defects, body shortening, and characteristic dorsal flexure of the posterior portion of the embryo [98]. Xdd1 acts as a dominant-negative mutant in the context of Wnt/β-catenin stimulation, yet Xdd1 does not impact Wnt/β-catenin-dependent mesoderm induction and differentiation; Xdd1 blocks convergent extension movements in dorsal marginal zone tissue, thus affecting the PCP-related process [98]. During gastrulation and neurulation, dorsal mesodermal and neuroepithelial cells extend mediolateral lamellipodia that facilitate directional cell movement toward the midline; injections of Xdd1 mRNA severely disrupt the polarity of these projections, interfering with the axis of cell elongation and ultimately affecting CE [96, 98, 99]. A Vangl2 mutation in the *Looptail* mouse was shown to affect CE of both mesoderm and neuroepithelium, causing a characteristic "looped" tail in heterozygotes and *craniorachischisis* in homozygous embryos [100]. CE underlies the morphogenesis of several other organs. For example, elongation of the cochlear duct along the longitudinal axis relies on CE and is disrupted in many PCP mouse mutants [81, 83].

In 2006, Park et al. observed shorter and sparser cilia in the epidermal multiciliated cells of *Xenopus laevis* embryos when the PCP effectors Inturned and Fuzzy were knocked down [76]. The phenotype of mice with homozygous knockout of Fuzzy or Inturned is similar to that of mice with mutation of core PCP genes (e.g., looped tail and cardiac outflow defects). However, Fuzzy and Inturned mutants also exhibit anomalies associated with defective cilia (e.g., cranial NTDs, polydactyly, and hydrochephalus). Mice with Fuzzy or Inturned mutations have short primary cilia [77, 78, 101, 102]. Core PCP proteins are involved in a variety of ciliary functions; knockdown of Dishevelled in *Xenopus* reduces cilial number and length and randomizes the position of basal bodies in frog multiciliated skin cells [103]. A compound mouse lacking all three mammalian Dvl homologues (Dvl1/2/3) exhibits similar defects in the position and orientation of basal bodies of motile cilia in ependymal and nodal cells [104, 105]. Homozygous mutations of Celsr2 and Celsr3 lead to severe hydrocephalus due to randomization of cerebral spinal fluid flow, due to a loss of uniform planar polarization of cilia in brain ependymal cells [106]. In a set of elegant experiments using *ex vivo* airway epithelial cell cultures, Vladar et al. showed that a set of PCP proteins contributes to ciliary functions by conveying information from the asymmetric PCP protein complexes at cell junctions to the microtubule and actin networks that define position of ciliary basal bodies [107]. Overall, asymmetric actin rearrangement, convergent extension, and function of cilia are among the crucial cellular processes regulated by PCP signaling during morphogenesis of organs.

4. Planar Cell Polarity Pathway and Kidney

Strong recent evidence now points to a role for PCP signaling in nephrogenesis and in maintenance of the adult kidney. For example, abnormally shaped, hypoplastic/dysplastic kidneys were found in homozygous Vangl2 or Fat4 mutant mice. This strongly suggests a requirement for PCP signaling during primary morphogenesis of the kidney. Interestingly, planar polarity during elongation of renal tubules (oriented cell division along the tubular plane) appears to be randomized in cystic kidney diseases linked to dysfunction of the primary cilium. Features of the PCP pathway during normal nephrogenesis and in the pathogenesis of renal cysts are discussed in detail below.

4.1. PCP Pathway and Early Kidney Development. Hypodysplastic, duplicated, and/or misshapen kidneys have been observed in mice with mutations in several PCP genes [108–110]. Hence, it is logical to assert that PCP signaling is required during early kidney development. Yun et al. recently showed that the PCP Wnt ligand, Wnt5a, is expressed in a graded manner at the posterior end of the intermediate mesenchyme [111]. Conditional ablation of Wnt5a in the intermediate mesenchyme prior to the UB outgrowth at E7.5 leads to bilateral duplication of ureters and duplex kidneys. Homozygous mutation of the PCP coreceptor, Ror2, also results in an extranumerary kidney phenotype, albeit at low frequency. Combining homozygous Ror2−/− inactivation with a heterozygous Wnt5a allele produces frequent duplex kidneys. Thus, noncanonical Wnt5a/Ror2 signaling is necessary for the earliest nephrogenic events such as patterning of the nephric cord and regulation of the initial UB outgrowth from the ND [111]. Wnt9b acts in both canonical and noncanonical Wnt signaling [20, 74]. Through its canonical function, Wnt9b regulates progenitor pool size and controls mesenchyme-to-epithelial transition that heralds differentiation of early nephron structures [20, 112]. As a PCP pathway ligand, Wnt9b is required for tubular elongation via CE [74]. Another PCP Wnt, Wnt11, is specifically expressed at the tips of each ureteric bud branch (UB). Targeted Wnt11 excision in the ureteric bud lineage leads to defective branching morphogenesis, precluding normal expression of Ret receptor in UB cells and the Ret ligand, GDNF, in the metanephric mesenchyme [113]. Reduced arborization of the UB ultimately translates into fewer nephrons since each UB tip provides inductive cues for conversion of the adjacent cap mesenchyme into a nephron [113]. The renal phenotype of either Wnt5a or Wnt11 mutant mice is reminiscent of the phenotypes observed in mice with deregulation of canonical Wnt/β-catenin pathway: for example, overexpression of β-catenin in mesonephric mesenchyme results in ND patterning defects, excessive expression of Ret, and extranumerary kidneys [21]; loss of β-catenin in UB reduces UB branching culminating in severe renal hypoplasia [22]. One possibility is that, during kidney development, Wnt5 and Wnt11 participate in both Wnt/β-catenin and PCP signaling. Indeed several Wnt molecules, including Wnt5a, were reported to act in both Wnt pathways [114] but the particular Wnt pathway activation seems to depend on unknown tissue-specific factors [115]. Another possibility is that the activities of the canonical Wnt and the PCP pathways are interdependent. For example, a hypermorphic allele of the canonical Wnt coreceptor lipoprotein receptor-related protein, Lrp6, increased Wnt canonical and, simultaneously, abolished PCP-induced JNK activities [117]. Several proteins have been shown to act as molecular switches between the Wnt/β-catenin and PCP signaling pathways [116, 118] lending credibility to this mechanism.

Kidneys of *Looptail* (*Lp*) E17.5-18.5 embryos are misshapen, smaller, and dysplastic (Figure 2(b)) [108, 109]. We showed that Vangl2 protein is expressed at high levels in the nephric duct and in metanephric epithelium derived from both mesenchymal and UB lineages during the embryonic period [119]. Yates et al. found a substantial defect in branching morphogenesis of E13.5 mutant Vangl2 kidneys: the kidneys were smaller and had ~25% fewer nephrons in homozygous and ~15% fewer nephrons in heterozygous *Lp* embryos; the proliferation index and apoptosis in wildtype and mutant *Lp*−/− renal tissues were equivalent [109]. Some abnormalities in actin distribution in *Lp*−/− cells were also observed, suggesting that actin dysregulation may affect changes in cell shape and/or cell motility needed for proper branching morphogenesis. Additionally, we identified a profound loss of the medullary zone and of tubular bundles in Vangl2 mutants, indicating potential defects in tubular elongation (Figure 2(b)).

Ye et al. described substantial renal hypoplasia (no sign of dysplasia) in targeted combined Fz4−/−; Fz8−/− mutants [120]. Both Fz4 and Fz8 participate in the PCP signaling and are expressed exclusively in UB branches. Their combined loss does not disturb mesenchyme-to-epithelial transition but affects the length of the ureteric bud prior to branching; no defects in cell proliferation or apoptosis were identified. A similar phenotype is seen in Pax2 heterozygotes where heightened apoptosis compromises UB branching and reduces final nephron number [121].

PTK7−/− embryos exhibit hypoplastic kidneys but detailed analysis of these kidneys is lacking [80]. Andreeva et al. recently found that PTK7 controls junctional localization of ROCK2 (a known PCP pathway participant), which is required for apical rearrangement of actomyosin and epithelial morphogenesis [122]. Saburi et al. reported that, in addition to dilated tubules (renal dysplasia), kidneys of Fat4−/− mice are also smaller. Of note, double Fat4−/−; Fjx−/− mutants produce ectopic ureters and duplicated kidneys at low frequency [110, 123]; the underlying mechanisms for smaller, extranumerary kidneys in this double mutant have not been elucidated in detail. In summary, deficiency of the PCP pathway leads to various kidneys anomalies which arise from the abnormal early nephrogenesis.

4.2. PCP and Glomerular Development. Podocytes are highly polarized renal glomerular cells that regulate formation of the glomerular ultrafiltrate. Podocytes develop in the proximal cleft of the S-shaped body from precursors that initially appear as typical cuboidal epithelia with tight junctions at the cell apex (reviewed in [41]). As differentiation proceeds, the cell-cell junctions migrate from the apical to the basal aspect of the cell and transform into unique sieve-like junctional complexes that connect adjacent "foot processes" (FPs) extending from neighboring cells. FPs contain precisely organized actomyosin bundles and form a unique alternating pattern such that a FP from one podocyte interacts only with a FP from the adjacent podocyte. Interdigitating FPs are arranged perpendicular to the axis of flow in the underlying capillary. Their slit diaphragms form the only points of contact between adjacent cells leaving the podocyte cell body to project into the urinary space. Mutations in slit diaphragm proteins lead to podocyte detachment and progressive glomerular dysfunction [41].

The role of the PCP pathway has recently been studied in glomerular podocytes. Babayeva et al. showed that components of the PCP pathway Vangl1, Vangl2, Prickle1, Scribble,

Dishevelled 2, and others are expressed in glomeruli and in cultured human and mouse podocytes [119]. It was further demonstrated that stimulation of cultured human or mouse podocytes with Wnt5a leads to an increase in both the average number of stress fibers and cellular protrusions per cell. Conversely, RNA interference-mediated depletion of Vangl2 in mouse and human podocytes leads to fewer stress fibers and projections per cell, a measure that can be correlated with FP structure *in vivo*. Loss of Vangl2 in cultured podocytes also results in redistribution of nephrin (a major slit diaphragm adhesion molecule) from the cell surface. In human embryonic kidney HEK293 cells expressing exogenous nephrin, loss of Vangl2 or stimulation with Wnt5a causes nephrin internalization via clathrin/β-arrestin-mediated endocytosis [108]. Vangl2 was shown to form a protein complex with nephrin [119].

Yates et al. and our group reported defects of glomerular development in *Lp* (Vangl2^{S464N}) mice: glomerular development was delayed compared to controls and a small proportion of *Lp* glomeruli exhibited collapsed tufts and signs of degeneration [108, 109]. Podocyte-specific Cre-LoxP-mediated abrogation of Vangl2 resulted in a similar glomerular developmental delay phenotype [124]. However, by the end of nephrogenesis at P14, a developmental "catch-up" seems to have occurred so that the glomeruli in either mutant or control mice looked similar, though mutant glomeruli were smaller and had fewer podocytes. Podocyte-specific loss of Vangl2 did not affect filtration function in adult kidneys: protein excretion at 12 months was comparable in both genotypes [124]. Yet, in the context of glomerular injury induced by heterologous anti-glomerular basement membrane (anti-GBM) antibody, the extent of injury was heightened and glomerular recovery was impaired in mutant versus control animals. This effect could not be attributed to the initial podocyte deficit in mutant glomeruli: postinjury loss of podocytes was increased in mutant mice, suggesting that Vangl2 is required for optimal podocyte recovery (e.g., via its effect on actin) and/or adhesion (via its effects on turnover of adhesion molecules). Importantly, anti-GBM injury greatly induced glomerular expression of many PCP transcripts indicating that PCP signaling is important for glomerular recovery after injury.

WT1 specifies podocyte fate and induces expression of Scribble in the developing and mature podocyte [125]; Scribble participates in the mammalian PCP pathway [81]. Hartleben et al. investigated the role of Scribble in the murine glomerulus using both podocyte-specific Cre-mediated Scribble knockout and the *circletail* mutant mouse (which expresses a shortened Scribble protein) [126]. In mice, Vangl2 and Scribble produce identical NTD and cochlear phenotypes and interact genetically and biochemically [79, 81]. Similarly, in zebrafish, both proteins act together to regulate neural tube formation [127]. Surprisingly, Hartleben et al. found no evidence that Scribble contributes to glomerular maturation or that it is required for filtration function under normal physiological conditions or after injury in mice [126]. These results suggest that the requirement for certain PCP genes may be tissue-specific. The differences between Vangl2 and Scribble glomerular phenotypes may lie in the fact that the latter is involved in the specification of basal features of apical-basal polarity. In podocytes, it may function in apical-basal polarity but not in polarity along the epithelial plane.

In mice, homozygous loss of Fat1, a giant atypical protocadherin homologous to the Drosophila Ft gene, leads to perinatal death [128]. Some mice also display holoprosencephaly and cyclopia, phenotypes often attributed to abnormal adhesion or defective Sonic Hedgehog signaling [129]. Light microscopic analysis showed no gross morphological abnormalities in Fat1 mutant kidneys; however, electron microscopy revealed a global loss of FPs and complete lack of slit diaphragms. The authors concluded that Fat1 acts as an important structural part of the slit diaphragm protein complex; its loss disrupts slit diaphragms and causes fetal congenital nephrotic syndrome [128]. During nephrogenesis, Fat1 is expressed at a high level in developing podocytes [130]. In rats with acute puromycin aminonucleoside nephrosis, expression of Fat1 protein increases after injury and concentrates in the new junctional contacts between podocytes that form after FPs are lost. The authors concluded that Fat1 may be involved in formation of initial contacts between adjacent podocytes during development and during the recovery phase after acute injury before the mature podocyte architecture is achieved [130].

4.3. PCP, Tubulogenesis, and Cystic Kidney Disease. Cystic kidney disease is a heterogenous group of human disorders characterized by the presence of dilated tubules and/or multiple macrocysts arising from foci along various segments of the renal tubule (extensively reviewed in [131, 132]). Among the many forms of hereditary renal cystic disease, the most common is autosomal-dominant polycystic kidney disease (ADPKD) associated with mutations of the *PKD1* or *PKD2* genes. Recessive forms of cystic kidney disease are caused by homozygous mutations of *PKHD1* (ARPKD) or genes associated with the Meckel-Gruber syndrome-Bardet-Biedl syndrome-nephronophthisis spectrum. The common feature of all mutant genes causing cystic renal disease (including *PKD1/2*) is that they encode proteins localized to the primary cilium and/or basal body; hence, these disorders are often referred to as ciliopathies (extensively reviewed in [133]). Ciliary membrane is enriched for receptors and channels which sense the extracellular milieu and transduce this information (chemosensation, mechanosensation, cell position along the epithelial tubule, etc.) into intracellular signals [134]. Components of many developmental pathways localize either at the basal body or along the ciliary membrane [135, 136]. Hence, it is not surprising that abnormalities of ciliary structure or function affect developmental signaling. Members of both Wnt/β-catenin and PCP pathways have been localized to the primary cilium [137]. However, the details of how cilia are linked to these two pathways are actively debated [138–140]. For the purpose of our review, we will focus primarily on empiric observations supporting a relationship between PCP proteins and cystic kidney disease and on the relationship of mutant cilia to dysfunctional PCP signaling during renal cyst formation.

In 2005, Simons et al. reported that inversin (encoded by the *NPHP2* gene mutated in humans with nephronophthisis type 2) acts as a molecular switch between the noncanonical and canonical Wnt/β-catenin signaling pathways during organogenesis [116]; an antagonistic relationship between these two pathways was suggested. Indeed, several recent publications presented convincing data documenting antagonistic relationship between Wnt/β-catenin activity and PCP signaling [117, 118]. The *inv/inv* mouse has cystic kidneys and laterality defects (*situs inversus)* [141], and knockdown of *inv* in zebrafish leads to a shortened anterior-posterior axis and widened somites, a classical manifestation of defective PCP signaling. Inversin contains several ankyrin-repeats and shares significant structural similarities with the *Drosophila* PCP protein Diego [142]. Like Diego, inversin interacts with PCP proteins Dvl and Vangl2 [116]. Based on the phenotypic features of *inv* zebrafish morphants, inversin protein structure and binding properties, it has been proposed that defective PCP may contribute to the pathogenesis of cystic kidney disease [116]. Previously, Bellache et al. had shown that intact PCP signaling is required for mitotic spindle orientation in Drosophila neuroblasts [143], and Gong et al. demonstrated that oriented cell division (OCD) was controlled by the PCP pathway in zebrafish [144]. Germino synthesized these observations into an elegant model whereby a cystic phenotype arises as a consequence of defective PCP signaling that disturbs cell division alignment in proliferating tubular cells [145]. According to this model, longitudinally oriented OCDs generate daughter cells that extend the tubule along its longitudinal axis while maintaining a constant tubular diameter [145]. Germino's model predicted that OCD would be lost in tubular cystic cells. In confirmation of this hypothesis, Fischer et al. demonstrated polarized longitudinal alignment of mitotic spindles in 95% of dividing renal tubular cells in young mice [146]. Importantly, these authors observed randomized orientation of cell divisions in dilated/cystic tubules of mice with inactivation of the Hepatic Nuclear Factor beta-1, *HNFβ1*, gene (*HNFβ1* is mutated in patients with diabetes and congenital cystic kidney disease [147]) and in *Pck* rat with polycystic kidneys [146]. This important work confirmed that the loss of OCD may contribute to cystogenesis. In subsequent years, numerous studies have examined the complex relationship between the PCP pathway, OCD, and cystogenesis [115, 131, 132].

The first experimental evidence implicating the PCP pathway directly in cystogenesis came in 2008 when Saburi et al. showed that loss of Fat4 (a homolog of the Drosophila PCP gene Fat) leads to a cystic kidney phenotype by embryonic day E16.5 [110]. In addition, Fat4 knockout mice display other characteristics of disturbed PCP such as defects of cochlear elongation, mild misorientation of stereociliary bundles within the Organ of Corti, curly tails, shortened body axis, and thickened neural tube; homozygous Fat4−/− mice die perinatally. The kidneys of Fat4−/− mice exhibit a loss of elongated collecting ducts and Loop of Henle, yet no change in proliferation or apoptosis of tubular cells was found. The authors detected randomized OCD in the Fat4−/− renal tubules and concluded that the loss of OCD underlies significant tubular dilation and renal cysts [110]. In subsequent work, Saburi et al. demonstrated that Fat4 genetically interacts with vertebrate Fat1 and Fat3 genes [123]. Although homozygous Fat1 or Fat3 mutant mice do not display tubular dilation or cysts, combined Fat1−/−; Fat4−/− double mutants have smaller kidneys with increased cystic phenotype compared to Fat4−/− animals. In addition, Fat1−/−; Fat4−/− mutants exhibit exencephaly (a phenotype not seen in mice with homozygous Fat mutations), shorter cochlear ducts, and defects in the alignment of cochlear hair cells [123]. On the other hand, Fat3 appears to antagonize Fat4 in the kidney and the combined Fat4−/−; Fat3−/− animals have a smaller cystic area than Fat4−/− pups. Intriguingly, the cystic and cranial NTD phenotype of Fat4−/−; Fat1−/− ani mals is reminiscent of the phenotype in mice and humans with mutations in certain ciliopathy genes (e.g., *Mks1*) [148, 149]. These observations suggest a potential role for Fat genes in the function of primary cilium. Indeed, Fat4 protein has been detected at the cilium [110], but its function there remains unknown.

Fat proteins may affect tissue PCP but may also function through the Hippo signaling pathway, which regulates tissue size by controlling cell proliferation, death, and differentiation [150]. This raises the possibility that the renal phenotype of Fat mutants may be due to disruption of the Hippo pathway. Indeed, loss of TAZ, the major downstream effector of Hippo pathway, results in polycystic kidneys [151]. Inappropriate activation of the Hippo pathway was detected in several mouse PKD models [152].

Saburi et al. reported that combining the Fat4−/− mutants with heterozygous mutations of the core PCP gene, Vangl2 (*Lp* mouse), exacerbates the cystic phenotype [110, 123]. Interestingly, we observed tubular dilation and occasional tubular or glomerular cysts in the E17.5 kidneys of homozygous *Lp* mice that bear a missense S464N mutation in the Vangl2 gene (Figure 2(b)) [108, 109]. Thus, Vangl2 may impact renal tubular development by affecting the primary cilium, OCD, or some other mechanism, but this remains controversial. Borovina et al. found defects in the alignment of ciliary basal bodies but not in the ciliary structure of primary cilia in pronephros and neural tube of the zebrafish Vangl2 mutant *trilobite* [153]. Similarly, Song et al. reported a disturbance of cilial tilting in the embryonic node of Vangl2−/−; Vangl1−/− embryos [154]; Antic et al. showed a loss of uniform cilial tilting in frogs with Vangl2 knockdown [155]. However, May-Simera et al. reported that knockdown of Vangl2 affects ciliary length in zebrafish [156]. Vangl2 protein was detected in the cilium of nasal epithelial cells [157] and we visualized a GFP-tagged Vangl2 protein in primary cilia of Madin-Derby collecting duct cells *in vitro* (unpublished results). Definitive proof for an effect of Vangl2 mutations on ciliary functions or OCD has not been established and it remains unclear whether loss of Vangl2 contributes to polycystic kidney disease. This issue awaits the generation of conditional mutants with a renal excision of Vangl2 that survives into the postnatal period.

Luyten et al. showed that tubular inactivation of *PKD1* in mature mice leads to cystogenesis, accompanied by loss of OCD and upregulation of the core PCP gene, Frizzled 3; elevated expression of Fz3 was noted in human ADPKD

tissue [158]. Fz3 protein is expressed at the primary cilium in cells lining renal cysts but not in sister cells along normal segments of the tubule. The authors concluded that Fz3 becomes activated in the absence of *PKD1*, leading to upregulation of Cdc42, rearrangements of actin, and loss of OCD [158]. Inappropriately elevated levels of Fz3 and randomized OCD were also detected in renal cysts induced by obstruction of the postnatal urinary tract [159].

Thorough examination of OCD in various mouse and rat models of polycystic kidney disease revealed a rather complex relationship between OCD, PCP, and cystogenesis. Bonnet et al. reported abnormal OCD in the tubules of young heterozygous *PKD1*−/+ mice; however, these mice develop only occasional cysts [160]. Humans with homozygous mutations of the *PKHD1* gene (ARPKD) have widespread tubular dilatation and macrocysts; mice with homozygous *PKHD1* mutations exhibit misaligned cell division in renal tubular cells, but curiously lack macrocysts in the kidney [161]. These observations suggest that PCP-dependent OCD may be disturbed in ARPKD but additional mechanisms may contribute to cystogenesis. In an elegant study by Karner et al., Wnt9b mutant mice were noted to have profound renal tubular dilation in the embryonic kidney [74]. Surprisingly, however, the authors discovered that cell division is oriented randomly in the embryonic period and mitotic spindles of dividing cells become polarized only postnatally during tubular elongation. Although cell number was normal in the dilated tubules of Wnt9b mutants, the ability of cells to undergo convergent extension was lost. Liu et al. reported that neonatal mice with the null mutation for another core PCP gene, Prickle1, exhibit tubular irregularities in various nephron compartments: proximal tubules were narrowed in the outer renal cortex and widened in the inner renal cortex; the cells of both collecting ducts and thick ascending loop of Henle were misshapen and misaligned [162]. At the cellular level, loss of Prickle1 led to the defective polarity of the renal tubular cells. Importantly, approximately 5% of the mutant Prickle1−/− kidneys appeared cystic at birth [162].

The mechanics of tubular cell intercalation was further examined by observation of multicellular rosettes during *Xenopus* renal tubulogenesis [163]. The tubular rosette structure is highly similar to the rosettes seen during the *Drosophila* germ band extension and involves shrinkage of a mediolateral cell-cell boundary to form a rosette, with subsequent resolution of the cell-cell boundary in the perpendicular direction to produce CE [164]. However, whereas the *Drosophila* germ band elongation is independent of PCP signaling and is primarily regulated by myosin II [164], overexpression of dexamethasone-inducible Xdd1 expression construct (which was previously shown to affect PCP functions) leads to shorter, wider tubular structures [163].

Based on the observations above, it is quite plausible that disturbance of OCD and/or CE contributes to cystogenesis. However, the PCP-dependent mechanisms influencing cyst formation may differ according to developmental phase. During the mid-embryonic phase in mice, mutations of cilial genes may cause defective CE, whereas during early postnatal tubular elongation (or after postnatal injury such as ureteral obstruction) [159] mutant cilial genes may disturb OCD. However, experimental proof for these temporally distinct PCP disturbances is lacking. While PCP clearly plays a role in tubulogenesis by facilitating both OCD and CE, the manner in which it is involved in human cystic kidney disease remains uncertain.

5. Concluding Remarks

Planar cell polarity genes were first identified in *Drosophila*, where pattern formation of extracellular appendages is easy to visualize. These genes encode a network of signaling molecules that reorganize the cytoskeleton to enable uniform localization of cellular structures. It is now well-established that mammals express homologues of fruit fly PCP genes and that PCP gene mutations disrupt key mammalian developmental processes such as neural tube closure and hair cell arrangement in the cochlea. On careful reflection, it is apparent that complex organs, such as the kidney, are organized along epithelial planes: cells of renal tubule are arranged so that dividing cells organize mitotic spindle alignment in the tubular plane to support linear tubular elongation; apical primary cilia are positioned and tilted uniformly to enable directional flow along the tubule to provide positional information; interdigitating podocyte foot processes are elegantly arranged along vascular flow through the capillaries which they envelop.

PCP gene homologs are expressed in the kidney and recent evidence has begun to uncover their functionality. Defects in branching morphogenesis were identified in *Lp* mice; this suggests that UB arborization relies on changes in cell shape [165], cell-cell adhesion, and movement [69]. In the future, it will be important to understand the role of Vangl2 and other PCP proteins in the behavior of UB tip cells and adjacent renal progenitor cells. In response to inductive WNT signals, progenitor cells must establish epithelial polarity, align themselves around a central lumen, and organize responses to the onset of directional tubular flow. At the same time, cells at the ureteric bud tip must undergo changes that support another round of branching morphogenesis. Thus, it is predictable that disturbance of PCP genes during this crucial phase would alter nephrogenesis. It will be important to understand how abrogation of PCP signaling in various cell lineages affects kidney development. The availability of Cre-LoxP-mediated PCP lines would certainly facilitate this task. Since unrestricted mutation of PCP genes may be embryonically lethal, the role of the PCP pathway in adult organs has been largely unexplored. Thus, conditional PCP gene knockout may provide missing information about the function of the PCP pathway in maintenance of adult kidney function as well.

Mutations of some PCP genes are associated with human neural tube defects [93]. Among NTD patients who survive into childhood, there is a high risk of developing progressive renal dysfunction. In the past, this has been attributed to secondary complications of neurogenic bladder rather than the possible renal manifestation of a primary PCP gene mutation. Interestingly, however, renal hypoplasia, duplicated collecting systems, and horseshoe kidneys have been reported

in NTD patients [166, 167]. Since PCP gene mutations cause renal malformations in mice, it may be timely to reconsider the etiology of renal problems in NTD patients [109].

While PCP is undoubtedly important for fly wings and mouse neural tubes, its potential importance in the kidney has largely been overlooked to date. From its role during ureteric bud branching and primary nephrogenesis to its involvement in the pathogenesis of congenital renal malformations and to the recovery from acquired renal disease in the adult, there is a great deal to learn about PCP in the kidney.

Conflict of Interests

The authors declare that they have no conflict of interests.

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