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The role of the Planar Cell Polarity Pathway in Kidney Development, Functions and Disease

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Abstract

Planar cell polarity (PCP) refers to the coordinated orientation of cells in tissue plane. Originally discovered and studied in *Drosophila melanogaster*, PCP is now widely recognized in vertebrates, where it has been implicated in organogenesis. Specific sets of PCP genes have been identified. The proteins encoded by these genes are organized into a dedicated signaling pathway, become asymmetrically distributed to opposite sides of each cell within a tissue plane and guide many processes that include changes in cell shape and polarity, collective cell movements or uniform distribution of cell appendages. A unifying characteristic of these changes is that they often involve actomyosin rearrangement. Mutations in PCP genes cause congenital malformations of multiple organs in many animals and, importantly, in humans.

In the last decade, strong evidence has accumulated for a role of the PCP pathway in kidney development. It has been proposed that defective PCP signaling contributes to polycystic kidney disease and that specific PCP gene mutations lead to Congenital Anomalies of the Kidney and Urinary Tract (CAKUT). In this review, we describe the origins, molecular constituents and cellular targets of PCP, with a special focus on the involvement of PCP molecules in normal kidney development and how their dysfunction leads to kidney disease.

Introduction

Unlike the easily appreciated apical-basal polarity of epithelial cells that refers to the asymmetry between top and bottom surfaces, planar cell polarity (PCP) reflects coordinated cell orientation in the plane of the tissue, i. e. in the direction perpendicular to the apical-basal axis. PCP has been recognized for decades by polarized arrays of bristles or hairs on the insect cuticle [1]. Genetic screens in *Drosophila* uncovered mutants with disorganized wing hairs or eye photoreceptors [2, 3], leading to the identification of a set of conserved "core" PCP genes [4]. These include *Frizzled (fz/Fzd)*, *Dishevelled (Dsh/Dvl)*, *Flamingo or Starry night (fmi or stan/Celsr)*, *Van Gogh or Strabismus (vang or stan/Vangl)*, *Prickle* (*pk/Pk*) and *Diego (dgo/Diversin or Inversin*) (fly name is followed by the vertebrate homologue name separated by "/") [5, 6]. The unifying characteristic of these genes is that

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encoded proteins are organized into complexes at opposing faces of epithelial cells [4]. For example, in the *Drosophila* wing, the Vang/Pk complex is seen at the proximal side of the cell, whereas the Fz/Dsh/Diego complex is located distally [7–10] (Fig. 1). An exception is Fmi, which partners with both the proximal Vang/Pk complex and the distal Dsh/Fz complex [11, 12]. Core PCP constituents are interdependent: mutations in any of them disrupt the localization of other core PCP proteins. The asymmetric localization of PCP protein complexes is crucial to the mechanisms by which they establish polarity along the epithelial plane and serves as a convincing marker of PCP signaling activity within the cell.

PCP has been associated with a specific signaling pathway regulating cell shape and behavior. Whereas PCP as a phenomenon refers to tissue-wide subcellular asymmetry that can be conferred by diverse mechanisms, we will largely discuss the mechanism mediated by core PCP proteins. Besides core PCP proteins, this pathway includes a large number of other players. Mutations in *Drosophila* genes encoding the atypical cadherins *Fat* (*ft/Fat*) and *Dachsous* (*ds/Dchs*) and the Golgi kinase *Four-jointed* (*ft/Fjt1*) [13–16] produce long-range defects in tissue polarization. The initial analysis of *ft* and *ds* fly mutants suggested that the encoded proteins function as upstream regulators of core PCP module, however, existing genetic evidence is also consistent with their independent role in PCP, at least in some context [17]. Overall, the upstream mechanisms that initiate asymmetric organization of core proteins may involve molecular gradients and mechanical forces, yet remain subject to debate.

Once the asymmetric distribution of core PCP proteins has been established, a set of downstream molecules encoded by PCP “effector” genes brings about changes in the cytoskeletal organization, cell adhesion and vesicular trafficking that drive directional movement and patterned tissue growth during organogenesis. Fly PCP effectors *Fuzzy (fy/Fuz)*[18]*), Inturned (in/In)* [19]*, Fritz* (*frt/Wdpcp*) [20] *and Multiple wing hairs* (*mwh*; vertebrate homolog is unknown) [3, 21, 22] control planar polarity of actin-based hairs, specifying the position and orientation of a single hair on each wing cell (Fig 1). In addition, certain house-keeping molecules, such as myosins, protein kinases and small GTPases, act downstream of Fz/Dsh to control cell shape and behavior, however, they may also regulate morphogenesis independently of core PCP- or Ft/Ds modules [23–26]. Recently, it has become clear that the initial classification of global, core and effector PCP genes does not fully reflect the complexity of the PCP pathway. For example, there is now evidence that Myosin II and other ‘downstream’ PCP effectors may act upstream of the core PCP proteins and influence their localization [16, 27, 22, 28, 29]. This feedback regulation is an essential feature of PCP signaling.

Another layer of complexity derives from the evolution of PCP homologs. While there are only two *frizzled* and *fat* genes and single copies of other core PCP genes in *Drosophila*, vertebrate genomes contain at least 10 *Frizzled* [30], 4 *Prickle*, 2 *Vang-like* [31], 3 *Fmi/Celsr* and 3 *Dsh/Dvl, as well as 4 Fat and 2 Dachsous genes.* As a result, the analysis of PCP in vertebrates may be hampered by genetic redundancies and overlapping functional drift. In contrast, the mammalian PCP effectors *Inturned*, *Fuzzy*, and *Fritz(WDPCP)* are encoded by single-copy genes (reviewed in [6]). For some vertebrate PCP players, such as *Daam1*, *Shroom3* [32–34] or noncanonical receptor tyrosine kinases *Ror1/2* [35–37], *Ryk* [38, 39] and *Ptk7*

[40], the corresponding *Drosophila* mutants lack obvious PCP phenotypes. Other vertebrate PCP regulators have acquired novel functions that may relate to the PCP pathway indirectly; for example, regulation of ciliogenesis [41–45]. Therefore, one goal of future studies is to understand whether the PCP molecules define a specific signaling pathway that orchestrates planar polarity or whether they also participate in a variety of events that are unrelated to PCP.

Importantly, loss of PCP signaling disturbs key morphogenetic processes such as cell migration, cell intercalation, constriction of apical surfaces, and oriented cell division (OCD) [46–51]. Other vertebrate-specific processes that require PCP components and contribute to three-dimensional body architecture are generation and function of motile and primary cilia as well as left-right patterning [52–57]. Thus, PCP signaling provides cells in a tissue with directional information that is needed for collective cell behaviors during organogenesis.

In the last 10–15 years, strong evidence has accumulated for a role of the PCP pathway in kidney development. Mutations of PCP genes have been associated with congenital malformations of the kidney and urinary tract in mice and humans [58] (Table). This review describes the origins of PCP signaling, its activity and cellular targets, with a particular emphasis on the function of the PCP pathway in normal kidney development and the consequences of PCP misregulation for kidney disease.

Origins of PCP

Phenotypic analysis of embryos carrying mutations in PCP genes has revealed the essential role of PCP components in many morphogenetic processes, such as neural tube closure or cardiac morphogenesis (reviewed in [6]). However, despite intense research for almost three decades, how PCP is established remains uncertain. In principle, since planar polarity can be visualized at the subcellular level [6], orientation of individual cells in embryonic tissues could originate from the intrinsic polarity of the zygote. However, PCP is normally detected in different tissues rather late in embryonic development and spreads over large distances that are comparable to embryo size. This suggests that PCP forms in response to a long-range cue(s) that is sensed and interpreted within each cell of the tissue. The small differences between individual cells are then amplified to allow robust planar polarization.

Global PCP cues

Molecular gradients are traditionally invoked to explain long-range cues for PCP. These could be gradients of transcriptional or enzymatic activity, cell-cell adhesion, extracellular matrix, or diffusible growth factors. Secreted Wnt proteins have long been considered excellent candidates for this role, due to their apparent ability to trigger the enrichment of Frizzled receptors at the closest surface of each responding cell [30, 59] (Box 1). Supporting this notion, Wnt ligands were found to be essential for PCP, serving as directional guidance cues in both *Drosophila* and vertebrates [37, 60–64]. Nevertheless, the involvement of Wnt ligands in PCP, especially in *Drosophila*, remains an ongoing debate [65–67]. It has been challenging to formally prove the role of Wnt ligands in PCP. For example, morphogen gradients could influence PCP indirectly, by affecting growth and tissue shape, which, in turn, might modulate the PCP vector [68, 69]. Alternatively, an initial positional cue in

early embryogenesis might propagate through the developing tissue by interactions between neighboring cells. Further research is needed to distinguish these mechanisms.

Graded adhesiveness is an alternative to the diffusible factor hypothesis. This idea is consistent with the demonstration of opposing activity gradients for the atypical cadherins Fat and Ds (reviewed in [16, 70]). The Golgi kinase *Four-jointed* phosphorylates the extracellular domains of these cadherins differently on each side of the cell, thereby increasing the affinity of Fat for Ds on one face and decreasing the affinity of Ds for Fat on the other. Thus, Four-jointed allows neighboring cells to polarize across the tissue (Fig 1). Gradients of Fat and Ds activity in the fly wing were originally thought to regulate fidelity of core PCP module-mediated signaling [13], but genetic evidence now argues that the pathway could also act independently of the core PCP module, in a context-restricted manner [71–73]. Notably, Fat/Ds signaling not only regulates PCP but also affects cell and tissue growth by controlling the Hippo pathway through an independent mechanism [16, 70].

Mechanical strain across the tissue might also serve as a global PCP cue [69, 74]. In the fly wing, planar polarized cells were proposed to realign in response to mechanical stress generated during the contraction of the hinge region [69]. Similarly, the force generated during blastopore closure in gastrulating frog embryos was suggested to align microtubules in frog ectoderm [74]. Consistent with this idea, artificially generated mechanical strain triggered microtubule polarization and altered PCP in frog ectoderm [74]. Similarly, in mouse skin explants subjected to uniaxial stretch, Celsr1, a homolog of Fmi, polarized according to the direction of tissue deformation [75]. Taken together, these studies suggest that PCP relies on mechanical forces. This hypothesis is further supported by the observations that the force generators, Myosin II and Rho-associated kinase (Rock), initially considered as PCP effectors [23], also function as key regulators of Vangl2 localization during neural tube closure in *Xenopus* [29] and the PCP during *Drosophila* germband extension; the latter involves a distinct molecular pathway [76, 77]. Whether the mechanical forces regulating PCP originate *within or outside* of the polarizing cells is unknown and warrants further investigation.

Local PCP amplification

Whatever the global PCP cues are, PCP is amplified at the cellular level by feedback interactions among core PCP proteins in the cytoplasm and at the cell surface. Initially, core PCP complexes form clusters in the cells that lack visible tissue polarity. At the next stage, the cytoplasmic constituents of opposing PCP complexes *antagonize* each other *within the same cell* [78], whereas the transmembrane components *positively reinforce* each other's localization across the junction *between two neighboring cells* [12, 79, 80]. These interactions often rely on post-translational modifications of core PCP proteins, of which phosphorylation is the most common. Vangl or Dvl are phosphorylated in response to Wnt signals and these modifications appear essential for PCP in the mouse limb or frog neural plate [29, 37, 81], and are conserved in *Drosophila* [82, 83]. Together, these mechanisms lead to the *asymmetric distribution* of core PCP proteins, a hallmark of active PCP signaling. Although the regulatory feedbacks are critical for initiation and maintenance of tissue polarity, they hinder our understanding of the sequence and causality of events which establish PCP.

In different epithelia, core PCP complexes initially form *molecular clusters* in a process reminiscent of membrane patch formation [84, 85]. These clusters are stabilized by molecular interactions within each protein complex, so that Prickle associates with Vang [7, 85] and Dsh is recruited by Fz [86, 87]. Recent data show that apicobasal polarity proteins enrich PCP complexes in the apical cell compartment and this may be essential for PCP signaling [29, 88, 89]. The apical protein Par3 is planar polarized in the *Xenopus* neural plate and recruits Pk3 to the apical surface to promote anterior PCP complex formation [90]. Interference with Par3 activity or with the binding between Par3 and Pk3 disturbs PCP in the neural plate. Notably, mutations of the basolateral determinant Scribble cause neural tube defects that are prototypical of core PCP mutants [91–93]. Although many physical and functional interactions between apicobasal and PCP proteins have been reported [94–96], the extent of crosstalk between different polarity modules remains to be fully appreciated.

The Fz-Dvl and Vang-Pk complexes are not usually present in the same location in the cell, suggesting that they are *mutually antagonistic* [10, 78, 79, 97] In the fly wing, the Vang/Pk complex becomes proximal, whereas Fz/Dsh complex accumulates distally (Fig 1). This negative feedback regulation commonly involves proteasome-mediated degradation of one core PCP component triggered by its interaction with a protein from the opposing PCP complex [81, 98, 99]. Specifically, Cullin1 and Smurf1 E3 ubiquitin ligases regulate Pk1 turnover in mice and flies in Fz- and Dvl-dependent manner, respectively [81, 98]. Similarly, *Drosophila* Prickle and Fz have been reported to promote each other's degradation [98, 100]. Alternatively, intracellular partitioning of PCP clusters is achieved by vesicular trafficking [26, 101–104]. In *Drosophila*, directional microtubule-dependent vesicular trafficking of Fz and Dsh to one side of the cell has been reported [105, 106]. Fmi is internalized more rapidly in Fz or Vang mutant cells [99], indicating that Fz/Fmi and Vang/Fmi complexes are selectively stabilized at the relevant junctions and more resistant to endocytosis. The importance of vesicular trafficking is highlighted by the requirement of several basic components of the endocytic machinery for PCP [26, 101, 107].

Drosophila mutant PCP clones often affect the polarity of an adjacent wild-type tissue, a phenomenon called *domineering nonautonomy* [108, 109]. This process is thought to reflect the formation of molecular bridges between the interacting cells due to a positive feedback. Extracellular domain of Fz on the distal side of one cell interacts with extracellular loops of Vang (likely in association with Fmi) on the proximal side of the neighboring cell, thereby coordinating polarity of individual cells in tissue plane [12, 79] (Fig 1). The asymmetric bridges may amplify PCP signaling by increasing the anisotropic adhesion of neighboring cells based on activities of Fmi/Celsr or Fat/Ds cadherins.

PCP signaling targets and mechanisms

Intracellular targets of PCP

Actomyosin complexes are crucial for cell contractility, directional membrane fusion and trafficking events underlying regulation of cell shape and motility; they are the key cellular targets of the PCP pathway. In *Drosophila* embryos, Myosin II activity is critical for the polarity of actin hairs in the wing as well as PCP during germband extension. In vertebrate embryos, actomyosin dynamics mediates most if not all PCP signaling effects

on morphogenetic behaviors, such as mediolateral and radial cell intercalations, apical constriction and oriented cell divisions (OCD). Whereas core PCP proteins have been implicated in actin remodeling and Myosin II activation mostly indirectly, several PCP effectors are well known to influence actomyosin dynamics. Mwh is a formin-like protein that negatively controls actin polymerization during hair formation in fly wing and legs [110, 111]. Inturned was proposed to function by binding to another formin protein, Daam1 [112]. *Fritz*/WDPCP is a WD40 domain protein [20] that affects F-actin by controlling septin localization [28, 113]. Depletion of different PCP proteins in vertebrate tissues leads to a reduced F-actin and decreased phosphorylation of regulatory myosin light chain (MLC) staining [114–117]. For example, reduction in phospho-MLC has been observed in *Ptk7*-mutant animals [117, 118]. Similar analysis is warranted for other PCP proteins. Besides actomyosin, noncentrosomal microtubules frequently align in a polarized array in epithelial tissues, and can mediate directional trafficking of PCP components [105, 106]. In frog ectoderm, this alignment has been associated with core PCP signaling [74]. In the fly, the directionality of apical microtubule arrays is instructed by Prickle isoforms [119 120]. Inactivation of *ft* and *ds* in *Drosophila* also leads to a loss of microtubule alignment and subsequent developmental phenotypes [14, 105].

Vesicular trafficking is another major intracellular target of PCP signaling [25, 26, 104, 107]. Both core PCP proteins and their putative effectors have been reported to influence Rab-dependent trafficking processes [25, 26, 104, 121]. Fuzzy contains a LONGIN domain, a common feature of SNARE proteins, that has been implicated in membrane fusion events [41, 42, 122]. Consistent with the role of Fuzzy in PCP, mouse embryos lacking Fuzzy function developed neural tube defects [123]. Cell junction remodeling coordinates PCP signaling-dependent cell movements within a tissue. Accordingly, PCP proteins have been physically linked to the apical and basolateral polarity regulators, including Par proteins, Lethal giant larvae and Scribble that regulate generation and maintenance of junctional complexes [90, 92, 94, 95]. Rearranging cell junctions inevitably causes cells to undergo cell intercalations and shape changes. Furthermore, PCP signaling affects cell adhesion through Fmi/Celsr, an atypical cadherin that binds both Vangl2 and Fz. The binding of Vang/Vangl2 and Fz to classical cadherins has been also described [25, 124–126]. The interaction of atypical cadherins Ft and Ds may also modulate adhesion strength between polarized cells in the plane of the tissue.

PCP regulation of coordinated cell behaviors

Whereas PCP proteins can control shape and motility of individual cells [36, 127–131], the primary function of PCP signaling is to regulate *collective cell behaviors* (Fig 2). Mediolateral cell intercalation, or convergent extension (CE), is a common mechanism of cell rearrangement [132–134]. During CE, neighboring cells elongate in the direction perpendicular to the axis of extension, form mediolaterally directed actin-based protrusions and intercalate to produce a longer and narrower tissue array. These mediolateral intercalations are blocked in embryos deficient in PCP signaling [48, 130, 135]. Both cell protrusive activity and junction remodeling are abnormal in the mutants, however, better understanding is hampered by the observations that overexpression and depletion of a PCP component often produce morphologically similar phenotypes (reviewed by [46]). Moreover,

since CE movements may be disrupted by defects in cell adhesion or growth factor signaling that is unrelated to PCP, the interpretation of these phenotypes can be ambiguous. Unlike CE, radial intercalations are oriented along the apicobasal axis. Radial intercalations are involved in lumen formation during tubulogenesis of multilayered epithelia (e. g. midgut or mammary gland)[136, 137], early epiboly and epidermal differentiation in *Xenopus* embryos [138].

Apical constriction, a process that involves shortening of apical cell junctions[139], also appears to involve PCP signaling, at least in some cases [115]. Apical constriction is a major cell behavior that is responsible for vertebrate neural fold formation [140, 141]. Although actomyosin contractility plays key roles in both apical constriction and CE movements, it is currently unknown why Myosin II activation causes some cells to converge and extend, but leads to constriction in other cells. Differential phosphorylation of MLC has been argued to determine actomyosin activation at different locations, such as apical versus basolateral cell junctions in an ascidian embryo [142]. Although PCP signaling takes place both apically and basolaterally, its spatially-restricted mechanisms remain to be further clarified [133, 142–144].

Oriented cell divisions (OCD) play a major role in axis elongation and organogenesis. OCD is an alignment of the mitotic spindles of dividing cells with the axis of tissue elongation. Since PCP dissolves during cell division, the dynamic regulation of protein localization is critical for PCP restoration at the end of each cell cycle. Indeed, Celsr1 phosphorylation in cells undergoing cell division was shown to be important for the dissolution and restoration of PCP [145, 146]. OCD has been linked to PCP signaling in both *Drosophila* and vertebrates [147–150]. In zebrafish embryos, PCP signaling-dependent OCD rather than convergent extension has been proposed to be a primary cause of body axis elongation [149, 150]. Supporting this view, mutations in PCP components affect OCD in many models [6, 148, 151, 152]. Although OCD phenotypes are frequently interpreted as a sign of deficient PCP signaling, dysfunction of apicobasal polarity components (reviewed by [136, 153]) or IFT proteins [154] can also lead to randomized OCDs.

PCP components and cilia

Cilia are specialized organelles at the apical surface of most cells where they direct fluid movements (motile cilia) or detect environmental cues that coordinate cellular behaviors during tissue morphogenesis or homeostasis (primary cilia) [155]. The PCP effectors Fuzzy, Inturned and Fritz/Wdpcp are critical for the formation of both motile cilia in Xenopus epidermis [41, 43] and primary cilia in frog and mouse tissues [28, 122, 156]. Loss of PCP effectors results in shortened, sparse cilia and disturbance of Shh [41, 157] or Wnt signaling [158]. PCP effectors were proposed to promote intraflagellar transport, possibly by regulating septin localization [28, 113] and the formation of the ciliary transition zone [159]. A recent study discovered that Fuzzy and Inturned function as a heteromeric GTPase effector for Rab23, a Rab GTPase involved in ciliary traffic [160], directly linking these PCP effectors to membrane trafficking and ciliogenesis.

The involvement of core PCP proteins in cilia biology is more complex. Some PCP proteins, such as Vangl homologues, do not seem to contribute to the formation of primary cilia, but their loss affects function of motile cilia in the mouse node [52], gastrocoel roof plate in

Xenopus [55] or Kupfer vesicle in zebrafish [54]. In these tissues, the sole motile cilium on each cell is posteriorly tilted, enabling a leftward directional movement of extraembryonic fluid that serves to establish left-right asymmetry in embryos [53]. Lack of Vangl function results in disorganized ciliary beating and randomized left-right axis [52, 54, 55]. Mutations in Celsr1, Vangl2 or Fz3 disrupt both radial (location within the cell) and planar (uniform tilting) polarization of motile multicilia on mouse ependymal cells, associated with disorganization of actin and microtubule cytoskeleton [161]. In some cases, the effects of PCP proteins on cilia have been linked to the centrosome/basal body that serves as a template for growing cilia [162]. Interestingly, mutations in Celsr2 or Celsr3 affect assembly of ependymal cilia through loss of centrosomal/basal body structures, causing lethal hydrocephalus in mice [163]. Inversin/Nephrocystin2 and Diversin (vertebrate homologues of Diego), and also Dvl2 and Prickle3 are all detected at the basal body in *Xenopus* or mammalian cells [164–167], where they may be required for normal centrosome/basal body structure and cilia formation [56, 57, 168–170]. It is currently unclear to what extent these proteins are involved in core PCP signaling and whether their centrosomal and ciliary functions are relevant for PCP. As discussed below, some of these mutants exhibit kidney anomalies that, in some cases, might be attributed to ciliary dysfunction.

In summary, the PCP pathway controls various intracellular processes and collective cell behaviors that are necessary for normal morphogenesis and maintenance of various tissues. Below, we detail the role of PCP signaling in development of the kidney and how mutations in genes encoding various PCP constituents lead to diverse kidney defects in mice and humans.

The PCP pathway and kidney development

Overview of mammalian kidney development

Development of the mammalian “metanephric” kidney starts at embryonic (E) day 9.5 in mice and at the 5th week of gestation in humans when a portion of the intermediate mesoderm on each side of the spinal cord undergoes mesenchymal-to-epithelial transition to form an epithelial tube, known as the nephric or Wolffian duct (ND), paralleled by a column of nephric cord [171]. As development proceeds, the ND induces a specialized renal progenitor cell population within the nephric cord, to convert into tubules and glomerulus-like structures, sequentially forming the pronephros and then, more caudally, the mesonephros. Although both are transient structures in mammals, the genetic programs that govern their development are similar to the events underlying development of the metanephric kidney, the final functional kidney in higher vertebrates, including mammals. Because of its simplicity (a single nephron), the *Xenopus* pronephros has been an informative model of processes involved in formation of the metanephric kidney [172]. The mammalian kidney is induced when caudal extension of the ND reaches the hindlimb level (Fig 3).There, signals from the nephric cord-derived metanephric mesenchyme (MM) stimulate lateral outgrowth of the ureteric bud (UB) from the ND [173, 174]; the descending ND/Wolffian duct subsequently gives rise to the reproductive system in males or degenerates in females [175]. As the UB contacts MM, it branches repeatedly to form a tree-like collecting system; a distal part of the collecting tree coalesces to form the renal pelvis and ureter. In a reciprocal

fashion, Wnt molecules secreted from each UB tip cause nearby MM cells to condense into a cap mesenchyme (CM) [171], containing nephrogenic progenitor cells (NPCs). In response to inductive UB signals, the NPC cells undergo mesenchyme-to-epithelial transition (MET) and are transformed into a polarized epithelium lining an early renal vesicle with a central lumen. The renal vesicle twists and elongates to form a comma- and then an S-shaped body, as specialized segments of the nephron emerge. At its proximal end, interaction with blood vessels forms a glomerulus that filters fluid into the nephron; the tubular fluid is modified as it passes through successive nephron segments. At its distal end, the S-shaped body fuses with its parent UB tip to form a continuous lumen leading to a common collecting duct that carries tubular fluid out of the kidney towards the bladder. The glomerular filtrate begins to flow at about E15 in mice when the ureter connects with the bladder. Fluid flow may provide mechanical cues that give upstream/downstream information to further orient tubular epithelial cells [176].

MM distant from the UB tip forms renal stroma that supports specification of the NPCs, development of nephrons and renal vasculature [177, 178]. Cycles of UB branching, local nephrogenesis and vascular recruitment are reiterated until ~38 week of gestation in humans, generating ~ 1 million nephrons per kidney [179]. In small rodents, nephrogenesis continues until postnatal day P7–10 generating ~ 10,000–40,000 nephrons per kidney [180]. Although no new nephrons are formed thereafter, postnatal proliferation of tubular cells drives tubular elongation and final anatomy and function of the renal cortex and medulla.

Development of the mammalian kidney is controlled by a hierarchical gene regulatory network which governs precise spatial and timely changes in cell fate, shape, polarity, proliferation, adhesion, directional cell movements, and expression of specific genes [171, 181]. Mutations in the key developmental genes that regulate these events lead to a wide spectrum of defects ranging from complete renal agenesis to hypoplastic/dysplastic kidneys to enlarged cystic kidneys (reviewed in [182, 183]). These diverse defects are collectively referred to as “Congenital Anomalies of Kidneys and Urinary Tract (CAKUT) that occur in 1 in 500 children worldwide [183]. The complexity of renal development makes it challenging to understand the molecular and cellular mechanisms that cause such diverse CAKUT phenotypes.

Expression of PCP constituents in the kidney

Many vertebrate homologs of the fly PCP genes are expressed in the developing mouse kidney. Core PCP proteins Vangl1, Vangl2, Pk1, Celsr1 as well as Ptk7 are all found in emerging nephrons and UB-derived structures [184, 185] and www.gudmap.org. Fat1 (a close homolog of Drosophila *Fat2* gene that regulates PCP during oogenesis [186]) is detected in UB[187] and, together with Vangl2, is highly expressed in developing podocytes; Fat1 persists in differentiated podocytes [188, 189]. Fat4 (the closest homolog of Drosophila gene *ft*) is found in the stroma surrounding CM while its interacting partner Dchs1 is expressed in progenitor cells at the outer edge of CM, where the interaction with Fat4 may take place [190, 191].

Several *Wnt* and *Frizzled (Fzd)* genes are expressed during kidney development, but it has been difficult to sort out the most important ligand/receptor pairs. In various cellular contexts, Wnt and Frizzled family members function in distinct canonical Wnt/β-catenin

or PCP pathways, depending on the involvement of specific co-receptors [192, 193]. The Wnt/β-catenin pathway plays critical roles in kidney development and disease (see Box 1, reviewed in [193, 194]), but will not be detailed here. Among the Wnt ligands that may signal through the PCP pathway, Wnt5a acts via the co-receptor Ror2 [195] and is expressed in a caudally-increasing gradient in intermediate mesenchyme [196, 197]. Wnt11 is restricted exclusively to the UB tip [198]. In contrast, Wnt9b is expressed in both the UB tip and the UB trunk, and Wnt7b is found only in the UB trunk [199, 200]. Frizzled 3, 4, 6 and 8, are detected in the UB-derived collecting duct [201, 202]. Thus, the distribution of specific Wnt and Frizzled molecules suggests that both short- and long-range signals may orchestrate PCP in the developing nephron.

Due to the existence of numerous PCP gene paralogs that are expressed in the kidney in complex patterns, it is difficult to infer their specific roles in nephrogenesis. However, the asymmetric distribution of PCP proteins in renal tubular cells indicates that the PCP pathway must be operative [201]: Fzd3 and Fzd6 proteins are found at the distal side of the tubular cells whereas Vangl1 is sequestered at the proximal side of the cell in E18.5-P1 mouse renal tubules (Fig 4). This PCP hallmark suggests that PCP signaling is active during embryonic and early post-natal kidney development

PCP components and the initiation of kidney development

Careful analysis of the elongating nephric duct in amphibians, fish and mice revealed convergent extension (CE) cell behavior, implying planar polarization of the ND cells [203, 204]. By injecting membrane-bound GFP, Lienkamp *et al* traced cell behavior in the proximal part of the pronephric duct in *Xenopus* tadpoles and showed that duct convergence and extension correlates with multicellular rosette formation [205]. This process relies on coordinated constriction and stretching of apical cell surfaces. Four to eight cells form rosettes, in which the long apical cell surfaces form wider rosette axis is oriented perpendicularly to the tubular plane. This is followed by shrinking of the rosette's wide axis. Subsequent stretching of apical surfaces of rosette cells occurs at the 90° angle, turning the rosette along tubular structure, thereby elongating the tubule longitudinally while narrowing its diameter (Fig 2). Importantly, expression of a mutant form of Disheveled (Xdd1) that can inhibit PCP signaling [48] disrupted directional rosette resolution resulting in wider and shorter proximal pronephros [205].

Xu *et al* implicated the mouse PCP gene *Ptk7* in elongation of the ND/Wolffian duct after UB outgrowth, as the duct becomes a part of the male reproductive system [206]. Loss of the *Ptk7* gene affected CE in rapidly proliferating Wolffian duct cells, leading to a short, less coiled duct with reduced sperm motility. Of note, mice with targeted knockout of *Ptk7* form kidneys, indicating that the ND has descended properly and UB outgrowth has occurred [40].

Wnt9b from the UB tip initiates metanephric mesenchymal cells to become nephrogenic progenitors [207]. Wnt9b activates Wnt4 in the precursor-derived pretubular aggregates, where Wnt4 controls mesenchyme-to-epithelial transition (MET) crucial for subsequent tubule development [208, 209]. Loss of Wnt4 blocks differentiation of renal epithelia precluding nephron formation [208]. Interestingly, Wnt4 controls MET in a β-catenin-independent manner [210], yet its association with PCP and PCP signaling has not been directly investigated.

Mice with *Wnt5a* deletions exhibit a range of kidney phenotypes from duplex kidneys (common), to hydronephrosis, to unilateral or bilateral renal agenesis (rare) [196, 197, 211]. Loss of the Wnt5a co-receptor Ror2 in collecting ducts causes duplex kidneys in ~ 50% of homozygous embryos, and over 85% of mice with *Ror2*+/−;*Wnt5a*+/− double heterozygous mutations exhibit duplicated ureter, unilateral or bilateral kidney agenesis. *Ror1* also genetically interacts with *Wnt5a*, resulting in ureter duplication and ectopic kidney in double heterozygous mutants [212]. The kidney phenotypes in *Wnt5a/Ror1* (or *Ror2*) mice are consistent with defective UB outgrowth linked to aberrant c-ret/GDNF signaling [213, 214]. Under guidance of GDNF from metanephric mesenchyme, ND expression of the GDNF receptor (c-Ret) is normally restricted to the site of UB outgrowth [174]. In *Wnt5a/Ror1–2* mice, ureter duplication is linked to elevated ectopic GDNF expression [197, 215]. Similarly, duplex kidneys in up ~40% of *Fat4*−/− embryos and ~70% of double homozygous *Fat4/Fjx1* embryos were reported [216]. Detailed studies revealed that the duplex kidney defect in *Fat4*−/− kidneys was caused by excessive c-Ret/GDNF signaling and was rescued by genetically removing one GDNF allele [216]. Unexpectedly, the researchers found that extracellular domains of Fat4 and c-Ret interact biochemically, providing an additional level of Fat4/c-Ret regulation [216]. Mice with mutations in the PCP effector gene *Wdpcp* also have ectopic kidneys [28], however, the precise underlying mechanisms have not been elucidated. Taken together, these observations suggest that PCP molecules may localize or control activity of growth factors that drive early kidney development; loss of PCP may account for defects in ND patterning and misplaced UB outgrowth that lead to anomalies, ranging from duplicated ureters to renal agenesis. Whether these PCP components participate in PCP signaling as a single molecular pathway or act independently during kidney development remains an important question for future studies.

PCP molecules and UB branching morphogenesis

UB branching is central to kidney development and requires coordinated changes in cell behavior (reviewed in [174, 217, 218]). Governed primarily by the GDNF/c-ret and FGF pathways, cells at the tip of each UB branch rapidly proliferate to form a UB ampoule [174, 219]. Dichotomous branching of the ampoule requires remodeling of the cytoskeleton, cell-cell junctions and cell-ECM adhesion, culminating in profound cell shape changes. Several mouse PCP mutants exhibit defective UB branching morphogenesis, confirming that PCP signaling is required for cell behaviors implicated in UB bifurcation [185, 220]. Hypo-dysplastic kidneys with fewer UB branches were found in homozygous E13.5 *Vangl2*$^{Lp/Lp}$ *"Looptail"* and *Celsr1* "*crash*" mutants; this phenotype was more severe in double heterozygous *Vangl2*$^{Lp/+;}$*Celsr1*$^{Crsh/+}$ embryos [220], confirming that these two genes interact genetically during kidney development as they do in neural tube and inner ear development [92]. Using optical projection tomography and 3D reconstruction, Brzoska *et al* showed that UB branching was particularly affected in the caudal aspects of E13.5 *Vangl2Lp/Lp, Celsr1Crash/Crsh* and *Vangl2Lp/+;Celcr1Crsh/+* kidneys 220, although the mechanism(s) underlying this predilection is unclear and may reflect shortening of the embryonic rostral-caudal axis due to deficient CE in these mutants [91, 92]. *Vangl2*$^{Lp/Lp}$ and *Celsr1*$^{Crsh/Crsh}$ animals also display reduced branching morphogenesis of the lung that is caused by defective cytoskeletal remodeling [51]. Actin polymerization defects were reported in *Vangl2*$^{Lp/Lp}$ kidney cells as well [185], suggesting that actomyosin deregulation

may contribute to reduced UB branching. Importantly, Vangl2 interacts with several PCP components, such as Dvl [221] and Ptk7, which have been linked to regulation of actomyosin contractility. Dvl activates the formin protein Daam1 that nucleates actin monomers and promotes actin polymerization [32, 222]. Daam1 downregulation in *Xenopus* embryos disrupts pronephric tubulogenesis [223]. Mice lacking the *Ptk7* gene develop renal hypoplasia, and *Ptk7* genetically interacts with *Vangl2* [40]. Ptk7 was shown to activate Src-ROCK2 signaling and modulate Myosin II contractility at cell-cell junctions in the inner ear cells [117, 118]. However, whether renal hypoplasia in *Ptk7*−/− mice is caused by actomyosin dysregulation in the UB cells is unclear.

PCP proteins remodel junctional complexes and ECM in flies [25, 224] and zebrafish [225, 226]. Similar mechanisms may account for *Wnt5a* mouse mutants with renal hypoplasia and UB branching defects associated with disorganization of basement membrane and reduced expression of laminin and type IV collagen in collecting duct cells [211]. Collectively, these studies indicate that PCP signaling is centrally involved in organizing cell shape changes and coordinated cell movements involved in UB branching morphogenesis.

PCP genes and nephrogenic progenitor cells (NPCs)

The NPC pool in condensing mesenchyme around each UB tip depends on cross-talk between the UB and its surrounding stroma [227, 228]. Absence of Wnt11 in the UB tips results in decreased attachment of NPCs to the UB tip, loss of polarized distribution of several markers within NPCs and a disruption of polarized cell behavior [229]. This causes a dispersion of NPCs from their niche and premature NPCs exhaustion leading to deficient UB branching and renal hypoplasia. Loss of stromal *Fat4* gene results in a dramatic expansion of the NPC pool at E12.5-E13.5 [228, 230], indicating that Fat4 non-autonomously inhibits NPC renewal (Fig 3). Similarly, loss of Fat4 ligands, Dchs1 or Dchs1/Dchs2, also expands the NPC pool [190, 191, 231]. The abnormal CM compartment in *Fat4*−/− or *Dchs1*−/− mice might affect UB branching by disturbing positional cues. Indeed, these mutants exhibit reduced UB branch number and abnormal shape and orientation of branches [191]. However, the signaling events contributing to NPC expansion are puzzling. *Vangl2*$^{Lp/Lp}$ mutant kidneys have normal NPC number; loss of one *Vangl2* allele in *Fat4*−/− kidneys does not exacerbate *Fat4*−/− NPC phenotype [190]. This argues against the involvement of the core PCP pathway in controlling NPC pool size. In various cellular contexts, Fat proteins activate both the PCP and Hippo pathways [16]. However, genetic removal of a *Yap* allele did not rescue the excessive NPC phenotype in *Fat4*−/− mice [190], indicating that Hippo signaling was not involved. Canonical Wnt/b-catenin pathway activity drives cell proliferation of renal NPCs [232], but was unchanged in *Fat4* and *Dchs1/2* mutants [190]. In conclusion, the core PCP pathway does not seem to control the NPC pool directly and the precise signaling events downstream of Fat4/Dchs in kidney progenitors require further investigation.

PCP molecules, tubulogenesis and pathogenesis of tubular cysts

In mice, renal tubule segments lengthen during embryogenesis, but there seems to be a secondary wave of tubular elongation in the early post-natal period. Tubular diameter of different segments is tightly controlled during this process. By carefully measuring tubular diameters in hundreds of circular transverse cross-sections of wildtype kidneys

from embryonic day 13.5 to postnatal day P5, Thomas Carroll's group has shown that the tubules become progressively narrower until late gestation; thereafter the tubular diameter is fixed [199]. The phase of tubular narrowing (convergence) occurs through a reduction in the number of cells surrounding each tubular lumen; cells intercalate along the tubular axis to extend the tubule (Fig 2 and 4). In E13.5-E19.5 tubules, cell divisions are randomized, but become oriented only after tubular diameter has been established around the time of birth [199]. Based on these results, the researchers proposed that tubular elongation is controlled by two temporally distinct, yet mechanistically connected, processes: CE during embryonic tubule narrowing and OCD after tubule diameter has been established postnatally. In *Wnt9b*−/− mice, tubules are dilated during the embryonic CE phase and become cystic postnatally. However, since Wnt9b acts in both β-catenin-dependent and β-catenin-independent pathways[199, 232], the mechanisms underlying cystogenesis in *Wnt9b*−/− mouse are likely complex. *Wnt7b*−/− kidneys lack normal tubular elongation in the medullary tubules; this defect was attributed to randomized OCD [200]. Notably, similar phenotype was found in the mice with deficiency of β-catenin in stroma [200], suggesting a paracrine action of Wnt7b through the Wnt/β-catenin pathway in the surrounding interstitium.

Mutations in several core PCP genes lead to tubular dilatation and occasional cysts. For example, embryonic kidneys of *Pk1*−/− mutant mice exhibit dilatation of renal cortical tubules while the medullary zone is hypoplastic. Marked cystic changes occur in ~ 5% of the mice [233]. Similarly, tubular dilation and medullary zone hypoplasia were reported in the *Ptk7*−/− kidneys [234]. E17.5–18.5 $Vangl2^{Lp/Lp}$ embryos display dilated proximal tubules and collecting ducts in the cortex, and significant loss of the medullary compartment [185, 220, 235]. Jeff Axelrod's group discovered that tubular diameters in E18.5 $Vangl2^{Lp/Lp}$, double *Fz3*−/−;*Fz6*−/− or in double kidney-specific *Vangl1*−/−;*Vangl2*−/− (*Vangl1,2DKO*) mutants were not as tightly regulated as in control kidneys [201]. Derish *et al* confirmed that tubular size was "relaxed" and the tubules were dilated due to defective CE in the E17.5 $Vangl2^{Lp/Lp}$ and $Vangl2^{\Delta/\Delta}$ (targeted knockout of Vangl2 exon4) kidneys [236]. Whether cell rosette rearrangement controls tubular diameter and drives elongation of mammalian renal tubules was not studied, but Derish *et al* reported abnormal apical cell constriction and reduced phosphorylation of Myosin light chain in *Vangl2* mutant tubular cells, consistent with such a possibility [236].

In 2006, Pontoglio's group demonstrated that tubular elongation is associated with OCD along the tubular plane in wildtype postnatal mice [237]. By measuring angles of mitotic spindles in neonatal *Hnf1β* mice (model of polycystic kidney disease (PKD) and Type I diabetes) and *Pck* rats (model of autosomal recessive PKD), the authors showed that OCD was randomized in pre-cystic dilated tubules of these animals and proposed that defective planar polarity underlies PKD [237] (Fig 4). This interesting idea was rapidly disseminated in several reviews [238, 239]. In 2008, McNeil's group showed that targeted deletion of *Fat4* leads to tubule dilatation and some cysts in E16.5 mouse kidneys via randomized OCD [240]. Removal of one *Fat1* copy in *Fat4*−/− mice further enhanced cyst appearance [187], confirming a redundant Fat1/Fat4 function in this context. Importantly, loss of one *Vangl2* allele on *Fat4*−/− background somewhat worsened the tubular phenotype, implying the potential involvement of PCP signaling However, since Fat proteins can also act via the Hippo pathway [16, 241], and there is now strong evidence that dysfunction of Hippo signaling causes

severe cystogenesis in mice and humans [238, 242, 243], the cysts seen in *Fat4*−/− kidneys are likely due to complex mechanisms.

The relationship between core PCP genes and cystic kidney disease was recently addressed experimentally. Conditional *Vangl1,2DKO* mice generated by Axelrod's group using Kif3a-Cre and Hoxb7-Cre deleters had a mild OCD defect at P1 [201]. Surprisingly, at 16 weeks of age, the mice displayed only minimally irregular tubules, with complete absence of cysts. Furthermore, cyst cells in conditional *Kif3a*−/− or ubiquitous *Pkhd*−/− mutants displayed asymmetric distribution of Vangl1 and Fzd6 proteins indicating that cystogenesis occurs despite normal core PCP module activity. Similarly, mutant mice with Hoxb7-Cre-driven excision of *Vangl2* had tubular dilatation and cysts at E17.5 and some residual tubular dilatation at P1. However, tubular dilatation disappeared by P7 [236] (Fig 4). Overall, these studies are consistent with a role for the core PCP pathway in establishing tubular diameter via CE, but do not provide a simple explanation for cystogenesis. The studies above suggest that additional molecular mechanisms operate around the time of birth to maintain renal tubule diameter.

What can drive the perinatal CE to OCD switch and what are the PCP pathway - independent mechanisms controlling tubular diameter? One possibility is postnatal ECM remodeling [244]. This might lead to changes in the tension between ECM and tubular cells, modulating both cell shape and cell movements required for CE [245]. With the onset of tubular flow at E15 in mice, mechanical forces on the primary cilium may also provide positional information that modulates ECM [246]. Although PCP signaling appears to control OCD, loss of cilia (as in *Ift88* zebrafish mutant [154]) or ciliary function (as in *Pck1* mutants [237]) also leads to OCD randomization. However, loss of OCD does not seem by itself to be sufficient for cyst initiation: e.g. randomized OCD in the *Pkhd1*−/− mouse does not cause cystic transformation whereas OCD is normal in the dilated tubules prior to cyst formation in the *Pkd1*−/− or *Pkd2*−/− mice [247]. Notably, the *Pkd1*-encoded protein, Polycystin1, binds to and stabilizes the junctional apicobasal polarity complex Par3/aPKC, regulating CE-like collective cell movements and cell polarity [248]. Thus cilia-dependent mechanisms may instruct both CE and OCD within renal tubules, independent of the core PCP module, yet alternative factors and mechanisms are needed to maintain tubular diameter in the postnatal period [248].

PCP molecules and glomerular development

Tubular fluid, an ultrafiltrate of blood, is generated by intracapillary pressure which drives plasma through specialized sieve-like cell-cell junctions between podocytes. During nephrogenesis, podocyte precursor cells initially appear cuboidal but rapidly develop actin-based projections, foot processes (FPs), that envelop the underlying capillary. FPs from neighboring podocytes interdigitate along the capillary in the plane tangential to blood flow (reviewed in [249]). Podocyte cell-cell junctions, initially found at the apical surface, descend toward the basal aspect of the cell to form highly-specialized slit diaphragms linked to the intracellular actin cytoskeleton. Each FP is anchored via focal adhesions to the underlying glomerular basement membrane. The highly polarized architecture of mature podocytes depends critically on actin cytoskeleton (Fig. 3).

Among the many fly PCP homologs expressed in podocytes [250], the giant cadherin *Fat1* is detected at an early stage, as nephron progenitor cells differentiate into podocyte precursors [251]. Fat1 was shown to participate in various cellular processes including PCP signaling together with Fat4 [187]. Fat1 depletion in cultured podocytes reduces cell adhesion and cell motility by decreasing activity of actin regulators Rac1/Cdc42, indicating its involvement in actin regulation [252]. Fat1 is a part of the slit diaphragm complex. Consistent with this role, neonatal *Fat1*−/− mice die due to the complete lack of slit diaphragms and widespread loss of FPs [189]. In rats recovering from puromycin aminonucleoside-induced nephrosis, elevated levels of Fat1 protein were found in the newly-formed contacts between podocytes [251], suggesting a role in recovery from injury by plausibly regulating actin cytoskeleton and FP assembly.

Vangl2 is highly expressed at the basolateral surface of podocyte precursors as they generate FPs [188]. Its loss inappropriately traps nephrin (the major structural slit diaphragm protein) at the cell membrane due to a defect in nephrin internalization [235]. Thus, Vangl2 is needed for the normal dynamics of cell junction remodeling and assembly of slit-diaphragms between newly formed FPs. As well, depletion of Vangl2 appears to change podocyte shape and reduces the number of filopodia and stress fibers, indicating that Vangl2 regulates podocyte actin cytoskeleton [235, 250]. Embryonic *Vangl2*$^{Lp/Lp}$ glomeruli are immature, have reduced podocyte number and may show collapse of the glomerular tuft [185, 188]. Adult mice with podocyte-specific excision of *Vangl2* have fewer podocytes per glomerulus, yet they have no sign of glomerular dysfunction under basal conditions[188]. However, following experimental glomerular injury, the mutant mice develop severe, permanent damage compared to the normal recovery of glomeruli in wildtype animals [188]. Thus, Vangl2 appears to contribute to podocyte survival and recovery, likely through its effects on actin cytoskeleton and slit-diaphragm remodeling.

PCP genes and human kidney disease

PCP gene mutations have been identified in a variety of human nephropathies (Table). Children born with neural tube defects (NTD) are at high risk for progressive renal dysfunction. For years, this was considered a secondary complication of the associated neurogenic bladder [253]. However, NTD patients often have CAKUT phenotype such as renal hypoplasia, duplex or horseshoe kidneys [185]; these congenital malformations arise *in utero*, well before bladder dysfunction could alter basic renal architecture. PCP gene mutations have been linked to human NTD [254]. The mutant animal models of the same PCP genes also have NTDs (e. g., *Vangl2*−/− or *Celsr1−/− mice* [31, 255]). Notably, these mutant animals display the spectrum of renal anomalies found in NTD patients. A plausible hypothesis is that the kidney abnormalities seen in NTD patients are attributable to abnormal PCP signaling.

Several PCP gene mutations cause Robinow syndrome that is characterized by pathognomonic facial dysmorphism and skeletal abnormalities [256–260]; hydronephrosis or renal dysplasia have been reported in some patients [261]. A *WNT5a* missense mutation was identified in a CAKUT patient with a unilateral duplex collecting system without skeletal defects [211], reflecting unilateral kidney duplication phenotype seen in *Wnt5a*

mutant mice [197, 212]. Mutations in both *FAT4* or *DCHS1* cause Van Maldergem syndrome featuring intellectual disability, craniofacial defects, hearing loss, skeletal malformations and, in some cases, renal hypoplasia [262]; the latter phenotype is consistent with kidney anomalies seen in *Fat4*−/− [240] and *Dchs1*−/− mice[191]. Homozygous truncating *FAT1* mutations were found in patients with a novel syndrome characterized by ocular abnormalities, nephropathy (glomerular- or glomerulotubular sclerosis), syndactyly and facial dysmorphism[263], while milder recessive mutations were identified in patients with various isolated glomerulopathies. These patients showed podocyte foot process effacement [252] similar to the podocyte abnormalities and lack of slit diaphragm in *Fat1*−/− mice [189]. Mutations in the PCP effectors *INTU*, *FUZZY* and *WDPCP* have been found in various ciliopathies, frequently with kidney involvement such as renal hypoplasia [43, 264, 265]. Again, mouse PCP effector mutants faithfully recapitulate many phenotypic features found in the patients [28, 43, 122, 123, 266]. Infantile Nephronopthisis type 2 (*NPHP2*, kidney microcysts and interstitial fibrosis) is due to mutations in *INVERSIN* [265]; the disease is likely caused by complex mechanisms that involve abnormal ciliary functions as well as disrupted canonical and non-canonical Wnt signaling [165].

Conclusions and future directions

PCP signaling is centrally involved in kidney development -- from outgrowth and branching morphogenesis of the UB to the patterning of the glomerulus, to shaping proximal and distal nephron segments, to the postnatal changes that organize and maintain renal functions. PCP gene mutations cause human kidney malformations in the CAKUT spectrum; experimental excision of PCP genes in mice leads to similar malformations and implicates the pathway in recovery from acute kidney injury after birth. However, many of the fundamental properties of the PCP pathway in the kidney are still unclear. The global signals that engage this pathway during nephrogenesis are largely unknown and the mechanisms that coordinate PCP with the cytoskeleton and apicobasal polarity are unexplored (Fig 5). The relationship of planar cell organization to directional flow of tubular fluid and transduction of mechanical signals by primary cilia or extracellular matrix represent interesting areas for future study. Although the pathogenesis of PKD does not seem to involve loss of core PCP pathway function [201], it may be related to dysfunction of other PCP pathway components (e.g. a Fat or the PCP effector proteins) via links to the Hippo pathway or cilia signaling and actomyosin dynamics. Presence of multiple PCP gene homologs expressed in the developing kidney, their potential functional redundancies or involvement in the non-PCP-related processes accounts for the difficulties of studying PCP in this organ. Polycystin 1 appears to regulate renal tubular CE and OCD through mechanisms that are independent of PCP signaling [248]. Thus, the PCP features may be disturbed indirectly in some nephropathies. To unravel these mechanisms, an approach that combines high-resolution live imaging in model organisms with *ex vivo* kidney explants or organoids carrying mutant PCP genes is needed. It is clear that more work is warranted to better understand the complexities of morphogenetic processes and PCP protein interactions involved in kidney development and the pathogenesis of the human disease. This review is just a starting point in that direction.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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BOX1:

WNT SIGNALING AND PCP

Wnt pathways promote cell proliferation, cell movements and cell fate specification during embryonic development [267]. The canonical Wnt/β-catenin pathway results in the stabilization of β-catenin in the nucleus leading to target gene activation. Wnt proteins also activate noncanonical pathways that are independent of β-catenin but can modulate core PCP components (Fz, Dvl, Pk and Vang) to trigger changes in cell shape and behavior. Noncanonical Wnt signaling is often referred to as the "Wnt/PCP pathway", based on several experimental observations. First, the core PCP component Frizzled is a Wnt ligand receptor [30]. Second, Dvl functions as a core PCP protein and as an obligatory player in the Wnt/β-catenin pathway. Third, some Wnt proteins and core PCP pathway components regulate cilia functions and left-right patterning [45, 61]. Finally, both Wnt and PCP signaling affect the localization or/and activity of apicobasal polarity components, such as apical Par proteins and the basolateral determinants Lgl/Scrib [92, 95].

Although these findings indicate that Wnt proteins can regulate PCP, the molecular mechanism is still lacking. Both canonical and noncanonical Wnt pathways, as well as core PCP protein stabilization, are accompanied by Dvl phosphorylation, but the modulation of cell shape and polarity involves RhoA GTPase, ROCK and Myosin activities, rather than β-catenin. Dvl phosphorylation leads to its association with the formin protein Daam1 and upregulation of RhoA and ROCK activity, followed by Myosin II phosphorylation [32, 114 268, 269]. Alternatively, in mouse limb buds, Vangl2 phosphorylation by Casein kinase I is initiated in response to Wnt5a and Ror2, a receptor tyrosine kinase, may be a key step in the regulation of Vangl2 localization [37]. The segregation of core protein complexes to opposite cell faces is achieved through positive and negative feedback loops to define cell and tissue polarity coordinates [6, 270].

Many Wnt proteins are expressed in the kidney in a precise temporal and spatial manner and are known to be the major regulators of kidney development. Thus, the crosstalk between Wnt and PCP pathways is one of the key mechanisms operating during different stages of kidney development.

BOX2:

PCP and the KIDNEY

The human kidney has a highly complex architecture: it is made of ~ 1 mln nephrons populated by more than 20 cell types. Each nephron forms an ultrafiltrate of plasma that flows through a series of specialized tubular segments that absorb or secrete small molecules and electrolytes to regulate body homeostasis. The kidneys produce growth factors and hormones that adjust our physiology. Extensive changes in cell polarity, shape, adhesion and cell division during embryonic development enable collective cell behaviors that arrange and shape tubular segments (reviewed in [271]). Apical-basal and planar cell polarity pathways in combination with mechanical forces set up the cell rearrangements and tissue coordinates that orchestrate morphogenesis.

Mutations in PCP genes have been associated with Congenital Anomalies of Kidney and Urinary Tract (CAKUT), including small, unilateral or horseshoe-shaped kidneys and polycystic kidney disease [185, 211, 261]. Collectively, CAKUT represent a common group of human congenital defects, but only one third of the causative genes have been identified. Pathogenic mutations in several PCP genes have also been well-documented in human neural tube defects, NTDs (reviewed [254]). Notably, NTDs are frequently associated with CAKUT, such as small or horseshoe kidneys [185]. Consistent with the role of mutant PCP genes in causing human CAKUT and NTDs, mouse mutants of the PCP genes Vangl2, Ptk7, or Celsr1 exhibit both neural tube and kidney abnormalities [40, 185, 188, 220].

For many years, defective PCP signaling was thought to initiate cystogenesis in the developing kidney, a key feature of polycystic kidney disease (PKD) [237, 238]. However, recent experimental data indicate that loss of core PCP genes leads to transient embryonic increase in nephric tubule diameter but does not result in postnatal kidney cysts[201, 236]. These observations largely refute the popular view that PCP defects are key to the pathogenesis of PKD in humans.

Bulleted points

- Planar cell polarity (PCP) refers to a coordinated cell organization across tissue plane and is appreciated in uniform patterns of scales on fish, trichomes (small hairs) on Drosophila wing or stereocilia in mammalian inner ear.
- Evolutionarily conserved PCP proteins function in the specialized PCP signaling pathway that controls coordinated changes in cell shape and behavior and commonly involves actomyosin activation.
- PCP proteins exhibit asymmetric subcellular localization along the tissue plane
- Many vertebrate homologues of fly PCP components participate in PCP signaling, but the analysis is more complex due to functional redundancy and/or additional roles in non-PCP related processes.
- Due to the essential roles of PCP proteins in morphogenetic processes, mutations in PCP genes cause congenital malformations of multiple organs and tissues.
- Mutations in the core PCP genes cause various kidney abnormalities, including dilatation of renal tubules, but do not lead to cyst formation.

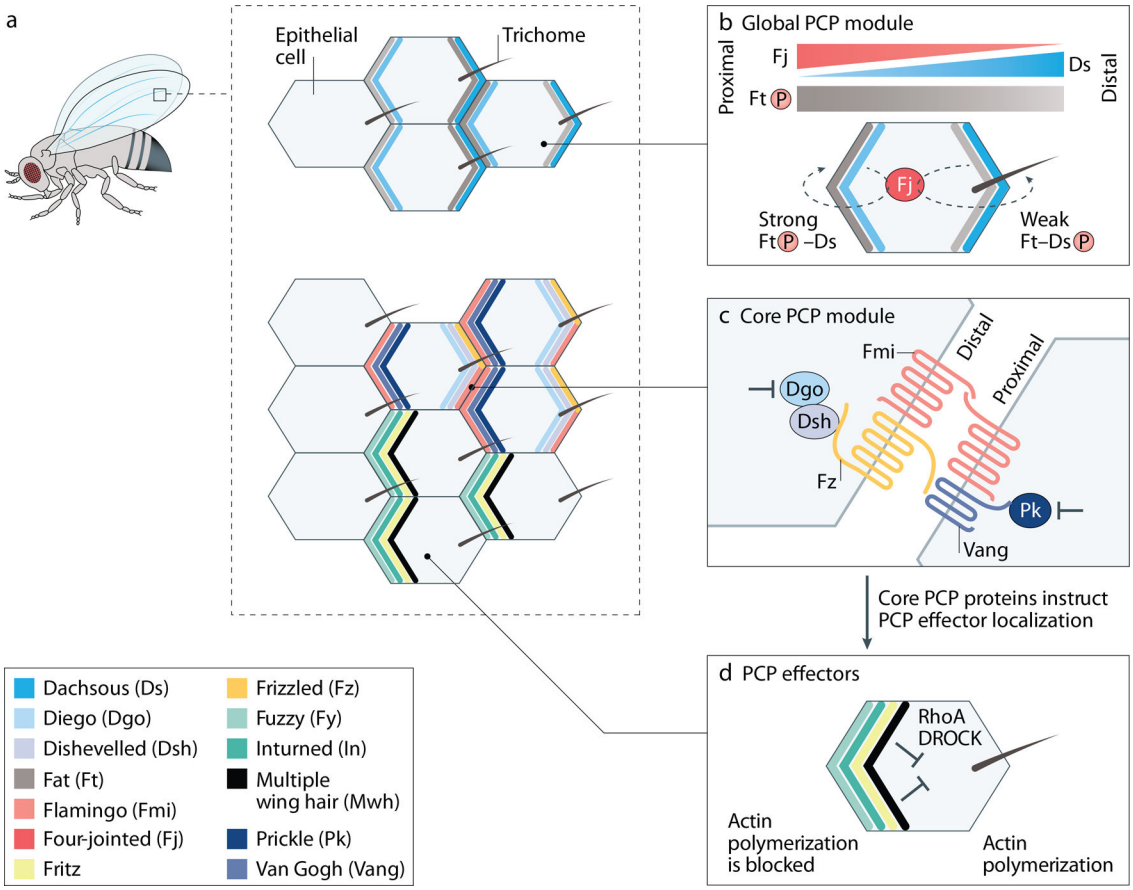

Figure 1: Planar cell polarity in Drosophila wing.

Left upper: Instructed by long-range cues, wing hexamer cells generate a single actin-based trichome (hair) at the most distal aspect of each cell. *Right upper: Fat* (*Ft*) mRNA is evenly expressed along the tissue, whereas *Dachsous* (*Ds*) transcript is expressed in a distal-proximal gradient and *Four-jointed* (*Fj*) kinase is expressed in a proximal-distal gradient. Fj phosphorylates both Ft (stronger phosphorylation at proximal side) and Ds (stronger phosphorylation at distal side). Strong Ft phosphorylation translates into a strong Ft-Ds protein-protein interactions at the proximal side, whereas Ds phosphorylation weakens Ft-Ds interactions at the distal part, thereby generating a shallow gradient of Ft-Ds activity across the tissue plane. *Right middle:* core PCP protein complexes are asymmetrically distributed: Vang-Pk to the proximal and Fz-Dsh-Dg to the distal sides. Cadherin Fmi is localized at both proximal and distal sides and forms homodimers between the extracellular domains of molecules expressed by adjacent cells. Interactions between Fmi and Vang or Fmi and Fz, as well as between extracellular domains of Vang and Fz expressed on surfaces of neighboring cells stabilize Vang-Pk and Fz-Dsh complexes on the opposite cell membranes. Inside the cell, mutual antagonism between Pk and Dsh creates “exclusion” zones where the proteins of the opposite core PCP complex cannot function. *Right lower:* Core PCP proteins control localization of PCP effectors via direct interactions (e.g. Vang interacts with In and Fy). In *Drosophila* wing cells, PCP effectors inhibit generation of trichome at the proximal side of the cell, whereas positive actin regulators, such as RhoA GTPase and *Drosophila*

RhoA kinase (DROCK) accumulate at the distal side of the cell where they promote actin polymerization and hair formation.

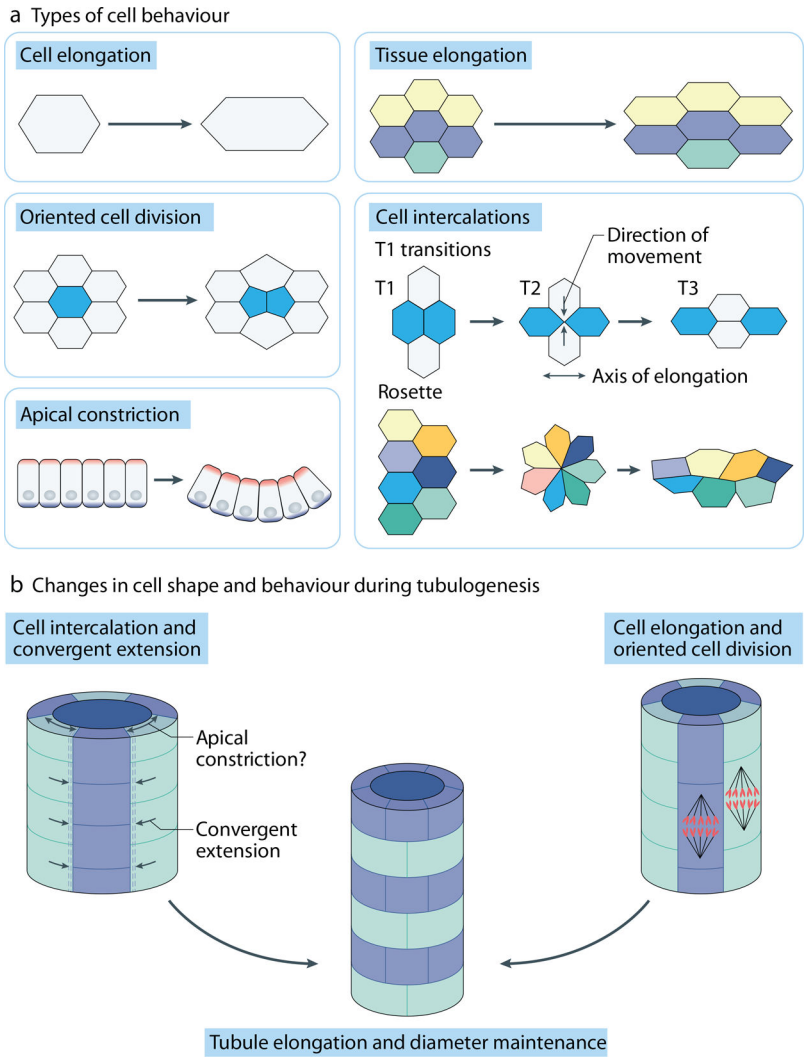

Figure 2: Cell behaviors during morphogenesis

(**A**) **Types of individual and collective cell behaviors that affect tissue architecture during morphogenesis**. Cell elongation and oriented cell divisions act to promote tissue extension or orchestrate branching events. Cell intercalations are mediated by so called T1 transitions that involve four neighboring cells and by more complex intermediate ‘rosettes’ that include 5 or more cells. Apical constriction affects the curvature of the folding tissue and can promote neighbor cell exchanges. (**B**) **Examples of cell behavior relevant to the formation of renal tubules**. Both cell elongation and oriented cell divisions can stimulate tubule lengthening. Cell intercalations that accompany convergent extension rely on elongation and polarization of cells in the medio-lateral direction perpendicular to the tubular axis. Both cell intercalation and apical constriction reduce tubule diameter and lead to tubule elongation. Oriented cell divisions enable incorporation of a daughter cell along the tubular axis, facilitating tubule lengthening

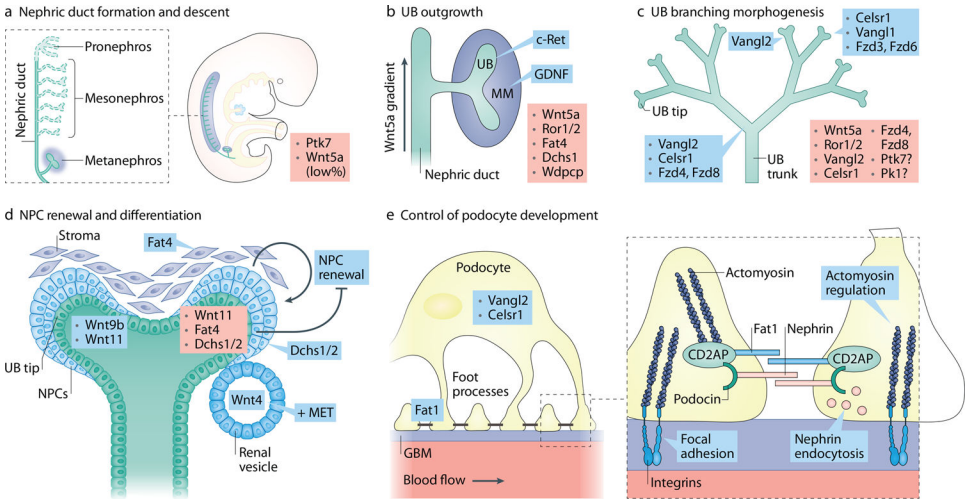

Figure 3: PCP signaling in kidney development.

(A). Nephric/Wolffian duct formation is affected by mutations in certain PCP genes; the known mutated PCP genes are shown in red on the right side of each panel. Expression of PCP genes participating in the discussed process is depicted when known. **(B).** Outgrowth of ureteric bud from nephric duct is largely controlled by c-Ret (expressed in the ND at the time of UB formation) and its ligand GDNF (expressed in the cells of metanephric mesenchyme. Loss or mutations in several PCP genes lead to abnormal UB outgrowth in both human and mice resulting in renal agenesis or kidney duplication. **(C).** Ureteric bud branching morphogenesis depends on timely and spatially coordinated changes in cell shape and movements. Mutations in PCP genes affect UB branching, branch shape and branching angles. **(D).** Nephrogenic progenitor cell renewal and differentiation depend on the crosstalk between stroma and UB tip. Loss of stroma-expressing Fat4 or of NPC-expressing Dchs1/2 leads to NPC expansion. The specific signaling events involving Fat4/Dchs1–2 are unclear. **(E).** Podocyte foot processes are interdigitated in a precise fashion along the glomerular capillary. Loss of core PCP protein Vangl2 and Celrs1 affects podocyte differentiation, nephrin internalization and glomerular maturation.

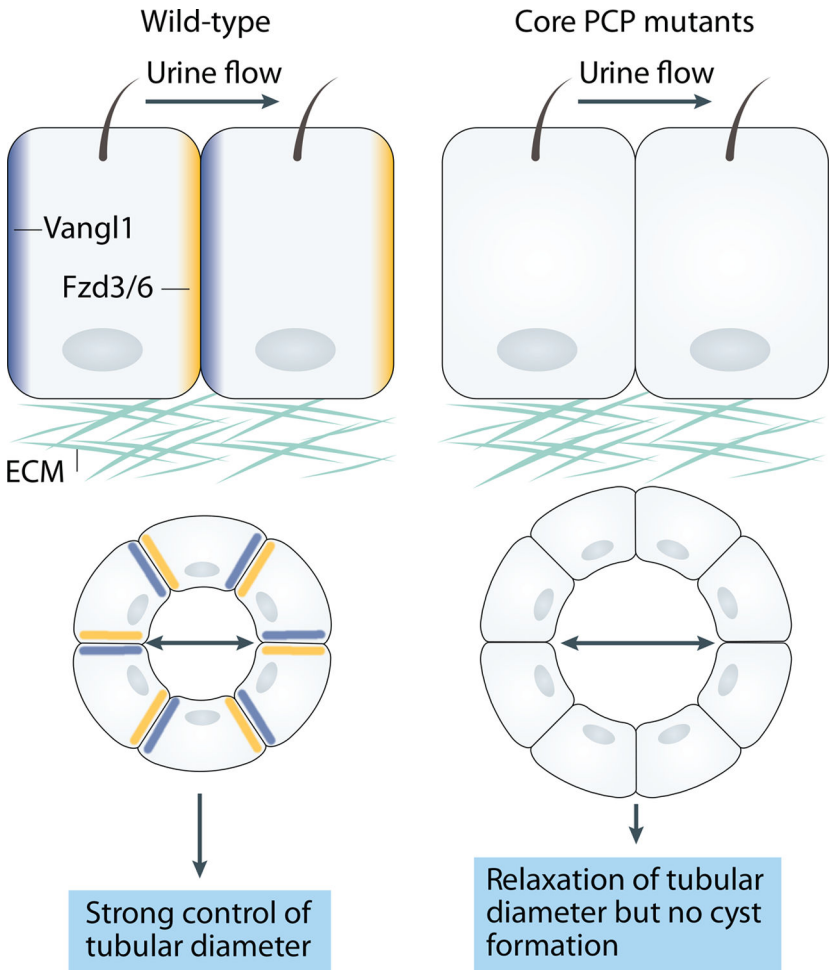

Figure 4. Relationship between PCP and cystogenesis.

Various mechanisms contribute to cyst formation in renal tubules including loss of cilia and/or ciliary function, increased cell proliferation or abnormal apical-basal polarity. It was also proposed that lack of PCP protein function might contribute to cystogenesis. Accumulated experimental data have shown that core PCP proteins are polarized along the tubular axis in the developing kidneys, and that PCP signaling tightly controls the tubular diameter via CE and OCD. However, loss of core PCP proteins does not lead to cyst formation.

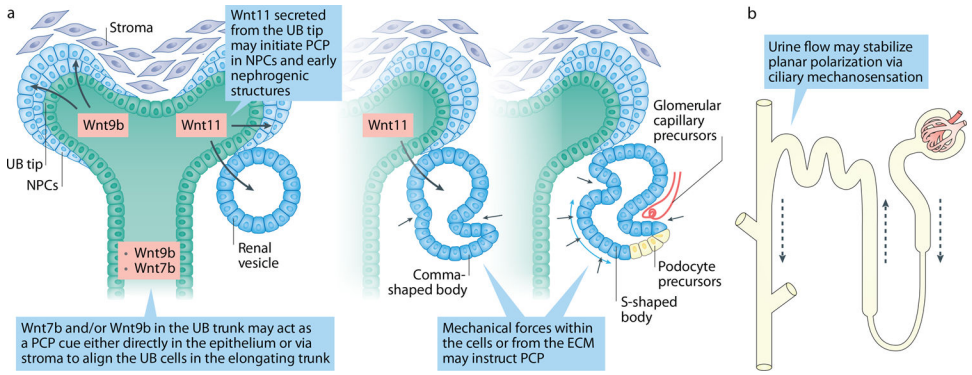

Figure 5. Potential instructive cues establishing PCP during kidney development.

The origin of PCP in early tubules is unknown, however, several molecules may potentially act as cues to initiate PCP in early nephrogenic structures. E.g. Wnt11 that expresses at the UB tip directs polarized NPC behaviors as they epithelize and transform into pre-tubular aggregates and renal vesicles. The link between apical-basal and PCP networks may coordinate establishment of planar polarization in the earliest structures. In the trunk, Wnt9b or Wnt7b may act locally in the UB trunk or non-autonomously on the cells adjacent to developing tubule to stabilize polarity of proliferating UB cells. Additionally, mechanical forces within the cells and/or from the ECM may provide polarity cues as comma- and S-shaped bodies undergo significant stretching and invagination. Onset of urine formation at E15.0 in the mouse nephron may provide further cues via ciliary mechanosensation to stabilize planar polarization along the growing tubule.