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The extracellular matrix and ciliary signaling

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Abstract

The primary cilium protrudes like an antenna from the cell surface, sensing mechanical and chemical cues provided in the cellular environment. In some tissue types, ciliary orientation to lumens allows response to fluid flow; in others, such as bone, ciliary protrusion into the extracellular matrix allows response to compression forces. The ciliary membrane contains receptors for Hedgehog, Wnt, Notch, and other potent growth factors, and in some instances also harbors integrin and cadherin family members, allowing receipt of a robust range of signals. A growing list of ciliopathies, arising from deficient formation or function of cilia includes both developmental defects and chronic, progressive disorders such as polycystic kidney disease (PKD); changes in ciliary function have been proposed to support cancer progression. Recent findings have revealed extensive signaling dialog between cilia and extracellular matrix (ECM), with defects in cilia associated with fibrosis in multiple contexts. Further, a growing number of proteins have been defined as possessing multiple roles in control of cilia and focal adhesion interactions with the ECM, further coordinating functionality. We summarize and discuss these recent findings.

1. Introduction

In vertebrates and other complex metazoans, tissue organization is achieved and supported through a dialog between extracellular signals and a trans-membrane interpretive machinery that coordinates appropriate assembly of intracellular cytoskeletal structures. Integrins mediate communication with the basement membrane; cadherins and desmosomal proteins mediate cell-cell communications. A growing number of studies now suggest that another structure, the cilium (Figure 1), also contributes to environmental sensing based on roles in receipt of mechanical and chemical cues. With rare exceptions (e.g., oncogenically transformed cells or lymphocytes, which are non-ciliated; lung epithelial cells, which are multiciliated [1]), most cells have a single protruding cilium. Although related structurally to the motile flagella of lower eukaryotes, such as *Chlamydomonas*, most cilia are non-motile, although again, rare exceptions of cells motile cilia exist, and some play important roles in development [2]. Structurally, a cilium is composed of 9 microtubule-based doublets organized in a circle around a hollow core, covered by a membrane, and extending 3–10 μm from the cell surface. The basal body which anchors the cell-proximal end of the cilium differentiates from the older (“mother”) centriole of the centrosome as cells enter G1 or G0 after cytokinesis, as cilia protrude from the cell [3]; cilia resorb, and the basal body is re-

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modified to function as part of a centrosome, in waves preceding S phase and G2/M. An excellent series of recent reviews have detailed ciliary ultrastructure, connections to cell cycle, and intracellular signaling defects associated with disease states [3–7].

In contrast to the broadly appreciated roles of cilia in receipt of flow or soluble cues, a growing body of literature connects ciliary function to control of cell adhesion, although the relationship has not been as broadly appreciated. While many cilia orient into lumens, others typically orient towards the extracellular matrix (ECM) (e.g. [8–12]). Receptors for many signaling proteins that influence cell adhesion, polarity, and interactions with the ECM localize expressly to the ciliary membrane; studies of “ciliopathies”, a group of hereditary diseases specifically associated with ciliary defects, clearly indicate aberrant cell-ECM interactions. We here summarize recent relevant studies.

2. The cilia is a platform for signaling by receptors that influence adhesion

Although the cilium is a relatively small structure, the ciliary membrane is the obligate site of action for receptors for some signaling systems that profoundly condition cell growth, morphology, and adhesion, and a specialized site of action for additional signaling receptors (Figure 2). To summarize some of the better-studied ciliary functions, the polycystins (PC1 and PC2 [13,14]) are encoded by the *PKD1* and *PKD2* genes, and are commonly mutated in autosomal dominant polycystic kidney disease (ADPKD). PC1 and PC2 heterodimerize on cilia oriented towards the lumen of renal tubules. In this system, the long extracellular domain of PC1 acts as a mechanosensor for fluid force [15], activating the PC2 calcium channel; loss of this signaling triggers cystic growth. The significant differences in ECM in renal tissue and typical extra-renal phenotypes associated with ADPKD (which include intracranial aneurysms and abdominal hernias) strongly suggest physiological roles for PC1 and PC2 in regulating normal cell adhesion and cell matrix deposition. Some studies have identified a population of PC1 as a member of the focal adhesion complex, which interacts with and regulates ECM proteins (summarized in [16]). In zebrafish, combined knockdown of pkd1 and pkd2 induced substantial collagen overexpression, which was an essential mediator of linked phenotypes of disrupted development [17].

The soluble ligand Hedgehog/Sonic Hedgehog (Hh/Shh) binds to its receptor Patched (Ptc) on the cilium, activating a signaling cascade that leads to activation of the Gli transcription factor family [18], which influences epithelial-mesenchymal transition (EMT) and matrix invasion. Some receptor tyrosine kinases, including notably PDGFRα, localize to and function at the cilia, where they act to guide directional cell migration and chemotaxis [19,20]. In some cell types, cilia display integrin receptors and the NG2 chondroitin sulfate proteoglycan (CSPG) [10,21], allowing response to ECM.

A pool of the developmental regulator Notch functions at cilia in epidermal differentiation. Notch regulates the balance between proliferation and differentiation in the developing epidermis, and loss of the primary cilium leads to disturbed Notch signaling, with subsequently compromised differentiation of the skin, and impaired skin barrier function [22]. Members of the nephrocystin protein group, targeted for mutation in the renal cystic syndrome nephronophthisis (NPHP), also localize to the cilia and transition zone. Some of these proteins (NPHP1, NPHP4) interact directly with and are regulated by focal adhesion-associated proteins such as Pyk2/PTK2B and p130Cas/BCAR1, and components of the planar cell polarity (PCP) machinery [23–27]; NPHP2, also known as inversin, enhances non-canonical Wnt pathway signaling, suppressing the canonical Wnt pathway [28]. Wnt/PCP receptors localize to the specific ciliary membrane; increasing cadherin adhesive activity during gastrulation induces Wnt/PCP pathway activity, which is necessary for normal assembly of fibronectin matrix [29]. Closer to the cell body, additional signaling

proteins with functions in regulation of interactions with the extracellular matrix localize to the ciliary basal body and adjacent transition zone. This includes another group of nephrocystins (e.g. NPHP6/CEP290 [30,31] and NPHP7/GLIS2 [32–34], and also proteins such as the HEF1/NEDD9 scaffolding protein [35], which induces ciliary resorption in response to extracellular cues.

3. Cilia-mediated response to ECM

The bulk of research on the effect of mechanical cues interpreted through cilia has dealt with organ systems in which cilia protrude into fluid-filled lumens or ventricles, or in tissue culture experiments with cilia pointing into the medium, with these stimuli either specifying directional migration during organogenesis, or polarized cell division, or programs of differentiation (e.g. [36–40]). However, a growing number of studies emphasize mechanical stimuli arising through ciliary interaction with the ECM. One particularly instructive system has involved the study of chondrocytes and joint development (Figure 3; discussed at length in [41]). As part of this process, columns of chondrocytes orient along the long axis of bone extension in the growth plate, with cilia binding to oriented collagen fibers through ciliary integrin receptors [10,42,43], with response to directional mechanical cues thought to specify directional production of ECM and development of tissue anisotropy [11]. Under normal growth, cilia-localized PC1 also mediates secondary cues such as elevated extracellular ATP induced indirectly by cellular interactions with collagen during matrix compression [44]. *Tg737/IFT88* (ORPK) mice, which have short or absent cilia, have both defects in skeletal patterning and stunted growth, associated with ECM deposition defects in the growth plate [45,46]. Kif3A mutant mice also lack cilia, and similarly have reduced proliferation and defective organization of chondrocytes, associated with accompanied by disorganized actin cytoskeleton and inappropriate localization of FAK to the focal adhesions [47]. Similar cartilage defects are seen in other “ciliopathies”, such as Bardet-Biedel Syndrome [48]; some recent reports have noted that loss of cilia is associated with early signs of osteoarthritis (e.g. [48,49]).

Besides chondrocytes, oriented cilia contact collagen fibers in tendons [12]; ciliary length, which conditions both cell cycle and activity of cilia associated signaling proteins [3,4], is highly responsive to tensile stress on tendons [50]. Intact cilia are necessary for the response of osteocytes to mechanical cues, with ciliary signaling necessary for activation of adenylyl cylase 6 (AC6) and transiently reduced cAMP [51–53]. One study has suggested that hair follicle development depends on interactions between cilia-localized Shh in dermal papilla with epithelially secreted laminin-511 in the basement membrane zone [54], although a subsequent study found contrasting results [55]; this question requires more investigation. In one fascinating recent study, both luminal epithelial cells and basal myoepithelial cells were ciliated at terminal end buds early in murine mammary development, with cilia decreasing on the epithelial cells as development progressed [56]. In these cases, cilia were oriented into the ECM and stroma, and Tg737 mutant mice with defective cilia had impaired branching morphogenesis [56], associated with enhanced canonical Wnt signaling and reduced Hh signaling in affected epithelial cells.

4. ECM changes in ciliopathies

Cilia are commonly structurally defective and ciliary signaling is disrupted in “ciliopathies” such as polycystic kidney disease (PKD), nephronophthisis (NPHP), Bardet-Biedl syndrome (BBS), and others, with these diseases characterized by abnormal cell-environment interactions. These defects commonly include extensive fibrosis within affected organs [57–62]. Characteristics of the fibrosis observed in cystic kidney diseases includes early changes in epithelial cell polarity and morphology, and evidence of altered interactions between

epithelial cells and stromal fibroblasts, followed by accumulation of ECM (collagen, specific laminins, and other proteins), and enhanced expression of matrix metalloproteases (MMPs) and TGFβ [60,63–67]. Deficient cilia-based signaling from polycystins and/or nephrocystins mutated in ciliopathies may contribute to altered integrin, ECM, and MMP activity based on indirectly transduced signals (see also [68–70]). However, besides their function at cilia, both polycystins and nephrocystins associate with proteins that regulate focal adhesion and cell-cell junctions, and have been reported to localize to these structures [23,25–27,71–77]: hence, it is possible that part of the fibrotic phenotype may arise from actions at these locations. Supporting a specific role for cilia, fibrosis also occurs in mouse models with experimentally induced defects specific to cilia [78–81].

Suggestively, deletion of the genes laminin-α5 [82] or xylosyltransferase 2 [83], required for proteoglycan synthesis, resulted in appearance of many of the classic phenotypes of polycystic kidney disease, and purified laminin V supported cyst growth [84], suggesting the fibrosis per se is an important mediator of renal cystic pathology. These observations have the potential to broaden the relevance of pathogenic ciliary-ECM interactions beyond the classic ciliopathies. For example, fibrosis is a common feature of many aggressive cancers, and actively promotes the disease process [85,86]. Cilia are commonly lost in oncogenically transformed cells, with the loss contributing to deregulation of signaling homeostasis [6]; and intriguingly, some proteins that are emerging as key regulators of ciliary integrity also function in cell-ECM interaction signaling, and are differentially regulated in cancer.

5. Control of ciliary dynamics by proteins with cell adhesion functions: emerging mechanisms

Over the past 4 years, a number of studies have elucidated the signaling machinery that controls ciliary protrusion and retraction during cell cycle, and has highlighted interactions with proteins that regulate cell adhesion (reviewed in part in [3,6]). A growing number of reports indicate that changes in ECM-interacting proteins and cell junctional proteins such as galectin-7, celsr2 and celsr3 specifically affect the process of ciliogenesis [87–89]. This ECM contribution is augmented by cytoskeletal signals emanating from within the cell. For example, RhoA-dependent reorganization of the actin cytoskeleton to form a polarized, apical web is essential for docking of the basal body and subsequent ciliogenesis [90]. In elegant work using micropatterned substrates, Pitaval and coworkers have addressed the long-known observation that high cell density is necessary for in vitro ciliogenesis, showing that the cue provided by compact cellular geometry for cilia formation involves modulation of the actin network to affect basal body positioning and cell polarization [91]. Providing some mechanistic explanation for these observations, Adams et al have shown that interactions between meckelin (MKS3, a ciliary protein mutated in the ciliopathy Meckel-Gruber syndrome) and the actin-binding protein filamin A is necessary for basal body positioning and ciliogenesis [92]. A high throughput screen for regulators of ciliogenesis has identified other regulators of the actin cytoskeleton, such as the gelsolin family proteins GSN and AVIL, and ARP3, a regulator of actin branching [93]. Action of the actin regulatory protein Missing-in-mitosis (MIM) in inhibiting Src phosphorylation of the focal adhesion protein cortactin is important for ciliogenesis, and for signaling of cilia-associated proteins such as hedgehog [94].

A number of the proteins regulating cell adhesion and ciliogenesis have well-documented connections to pathological conditions such as cancer. For example, NEDD9 is best known as a CAS family protein that localizes prominently to focal adhesions, and mediates integrin signaling and cell attachment to matrix; further, upregulation of NEDD9 commonly occurs in and drives invasive and metastatic cancers, and causes EMT, secretion of MMPs, and altered ECM [95–97]. Transiently induced expression of NEDD9/HEF1, and concomitant

activation of the Aurora-A kinase (AURKA) at the basal body induces ciliary resorption [35]. This activation process includes binding of Ca^{2+}-liganded calmodulin to AURKA, promoting the AURKA-NEDD9 interaction [98]; as AURKA has recently also been found to bi-directionally signal with the PC2 calcium channel [99,100], these interactions may similarly affect PC1/PC2-dependent cell adhesion processes. NEDD9 inducing ciliary resorption can also contribute to its role in carcinogenesis by deregulating cell migration and proliferation, as cilia have been shown to be required for oriented cell migration with cilia pointing into the direction of cell migration [19], and as ciliary disassembly has been proposed to stimulate cell cycle progression (reviewed in [3]). Conversely, the von Hippel-Lindau protein (VHL) supports ciliary extension and maintenance, with supporting activity provided by glycogen synthase kinase 3β (GSK3β) [101]. Loss of VHL is a driver oncogenic lesion for the significant majority of clear cell renal cell carcinomas [102], induces expression of NEDD9 and AURKA [103], and also induces fibrosis and accumulation of cysts [104,105]. Besides its role at cilia, VHL also controls other cellular signaling pathways through its function as a ubiquitin ligase that controls the abundance of hypoxia inducible factors (HIFs) and their resulting transcriptional targets; as with NEDD9 and AURKA, the multiplicity of affected pathways makes it difficult to specifically ascribe altered cell growth phenotypes to roles in regulating cilia or alternative processes. Finally, the adenomatous polyposis coli (APC) tumor suppressor is mutated in many cancers, and also in heredited syndromes characterized by cyst growth and fibrosis; in Gardner's syndrome, familial mutations in APC have recently been suggested to have features of ciliopathies [106]. The relationship between cancer, cilia, and ECM requires more study.

6. Conclusion

In conclusion, evidence continues to amass in support of the idea that the cilia plays an important role in cellular homeostasis, based on its ability to integrate chemical cues and flow and compression forces. Disruptions in cilia deregulate cell growth and polarity, and produce an extracellular environment, and frequent fibrosis (Figure 4). In turn, disruptions in the extracellular environment alter the signals received by cilia, again influencing cell growth properties. Given the rapidly increasing appreciation of ciliary localization and function of signaling proteins that have long been known to have important regulatory roles in cancer and other diseases, future studies should pay heed to the role of this organellar antenna in ensuring proper receipt and dispersion of growth signals.

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• of special interest

•• of outstanding interest

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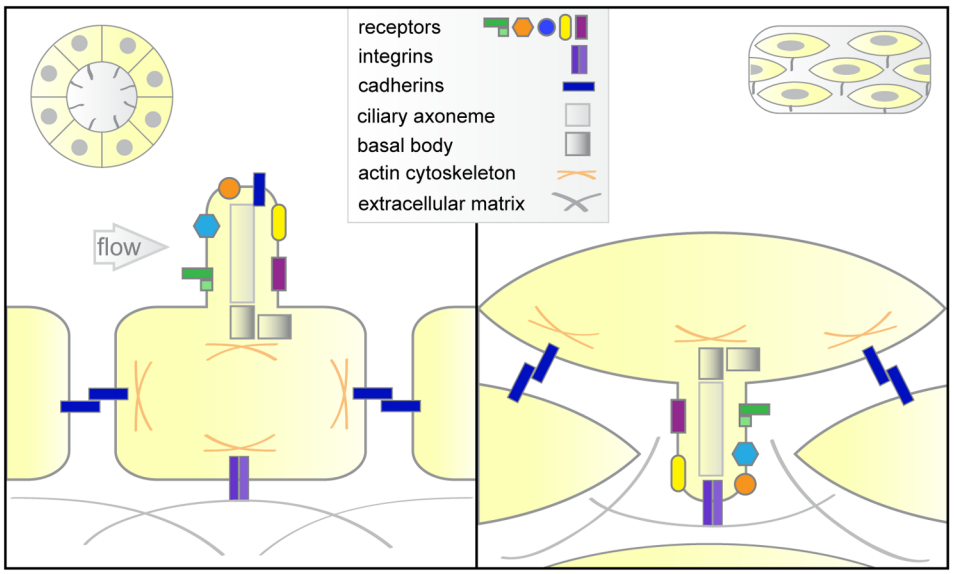

Figure 1. Environmental sensing in ciliated cells.<
br>In some cell and tissue types, as in renal tubules, cilia protrude into lumens (left panel), while in others, such as connective tissue, cilia extend towards the extracellular matrix (ECM) (right panel). Multiple receptors for soluble growth factors or for mechanosensory stimuli (e.g. fluid flow) localize to the ciliary membrane, controlling signaling cascades that influence cell proliferation, polarity, and interaction with the ECM. Some canonical cell adhesion receptors, including cadherins, and integrins, have been shown to be themselves localized to the cilium in some cell types [8,10,107,108]. Some basal body-localized proteins with ciliary functions also regulate the actin cytoskeleton [92,94,109].

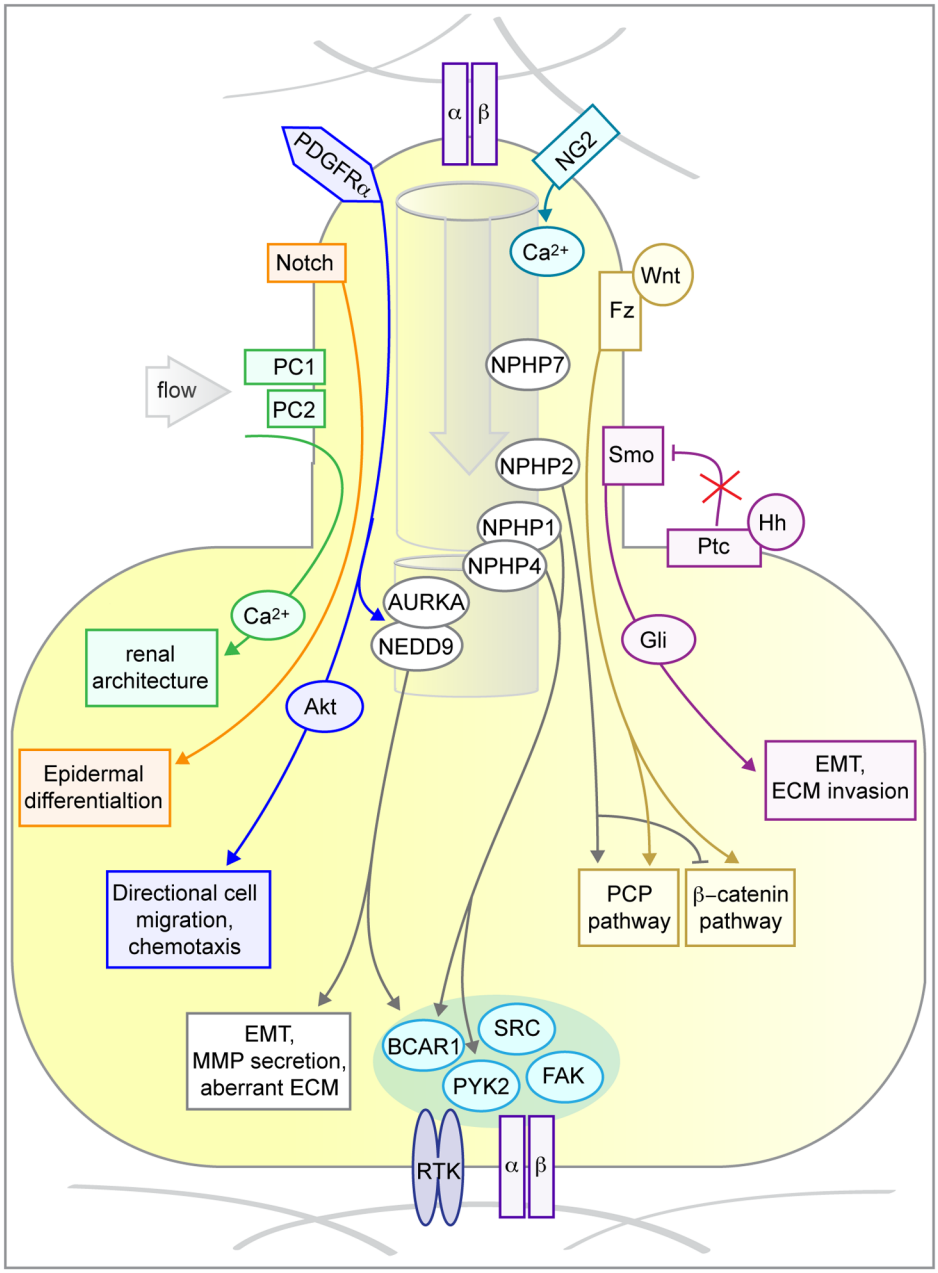

Figure 2. Signaling of the cilium influencing ECM interaction and planar cell polarity

The specialized ciliary membrane displays receptors for proteins that influence the ECM interactions, epithelial-mesencymal transition (EMT), and planar cell polarity (PCP). The polycystin PC1/PC2 heterodimer is a mechanosensor that responses to fluid flow by changing activity of the PC2 Ca^{2+} channel, controlling intracellular Ca^{2+}, and regulating signaling important for the integrity of renal architecture [15]. During epidermal development, the commitment of progenitor cells to differentiate relies on Notch signaling, with a pool of Notch functioning at the cilium [22]. In quiescent fibroblasts, basal body-localized PDGFRα mediates signals for directional cell migration and chemotaxis through activation of Akt [19,20]. In chondrocytes, integrins (αβ) and NG2 chondroitin sulfate proteoglycan (NG2) interact with ECM at the ciliary membrane [8,10,110] with integrins

shown to potentiate fibronectin-induced Ca^{2+} response [21]. Hedgehog (Hh) signaling relies on the primary cilium; the Hh receptor Patched (Ptc) is removed from the cilia membrane following Hh binding, allowing Smoothened (Smo) to enter the ciliary membrane, which in turn activates the Gli transcription factor family, promoting EMT and ECM invasion [111]. The Wnt receptor Frizzled (Fz) is present in the cilium, and accumulated in cystic epithelia [112]; downstream of Wnt, cilia-based suppression of canonical β-catenin versus activation of non-canonic PCP signaling are influenced by the nephrocystin NPHP2 [28]. Other nephrocystins localized to the transition zone (NPHP1, NPHP4) can interact with adhesion-associated proteins including BCAR1/p130Cas and PYK2 and PCP effectors [23–27]. Knockdown of the ciliary protein NPHP7 leads to severe renal fibrosis. NEDD9/HEF1 and Aurora A (AURKA) are localized at the basal body initiating ciliary disassembly [35], but also influence focal adhesion signaling and secretion of MMPs via interactions with SRC and FAK [95–97].

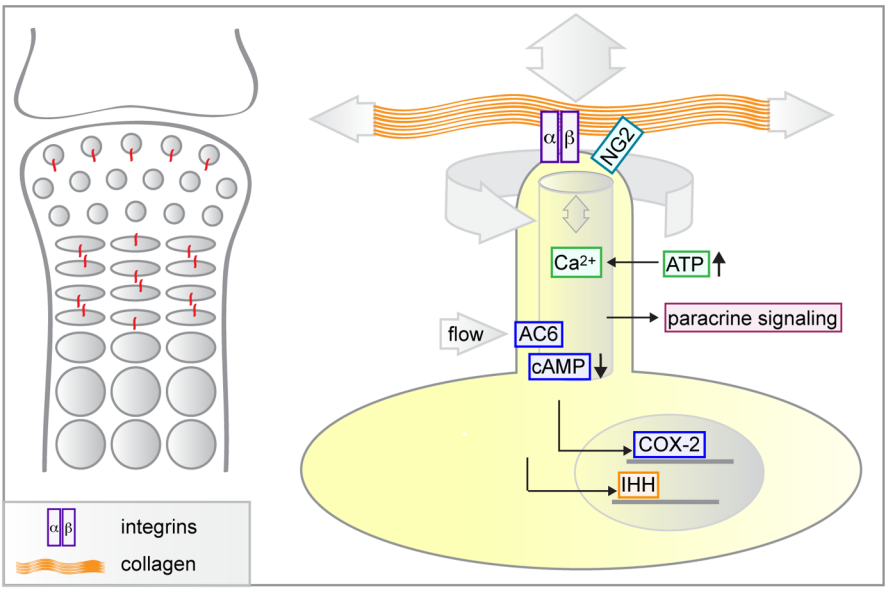

Figure 3. Ciliary signaling in cartilage and bone cells

Articular chondrocytes sense mechanical forces including shear stress, rotation, pressure, and tension in part through interactions of the ECM with ciliary integrins and NG2 chondroitin sulfate proteoglycan [10,43,113] with responses supporting development of tissue anisotropy. In load-bearing areas of the bone, cilia of nonproliferative superficial cells at the articular surface projecting away from the surface, whereas columns of proliferating cells (e.g. like growth plate chondrocytes) can be oriented towards or away from the articular surface [11,43,45]. A compression-induced Ca^{2+} signaling response mediated by ATP release relies on cilia integrity [44]. Hydrostatic loading of growth plate chondrocytes increases Indian hedgehog (IHH) signaling, governing chondrocyte proliferation and differentiation in the growth plate dependent on intact cilia [114]. Cilia are required for osteogenic and bone resorptive responses to fluid flow, but in contrast to other tissues, these responses do not require Ca^{2+} [52]. In osteocytes, fluid flow leads to a decrease of cAMP dependent on ciliary AC6, which induces COX-2 gene expression [51]. Paracrine signaling by mechanically stimulated osteocytes relies on cilia [53].

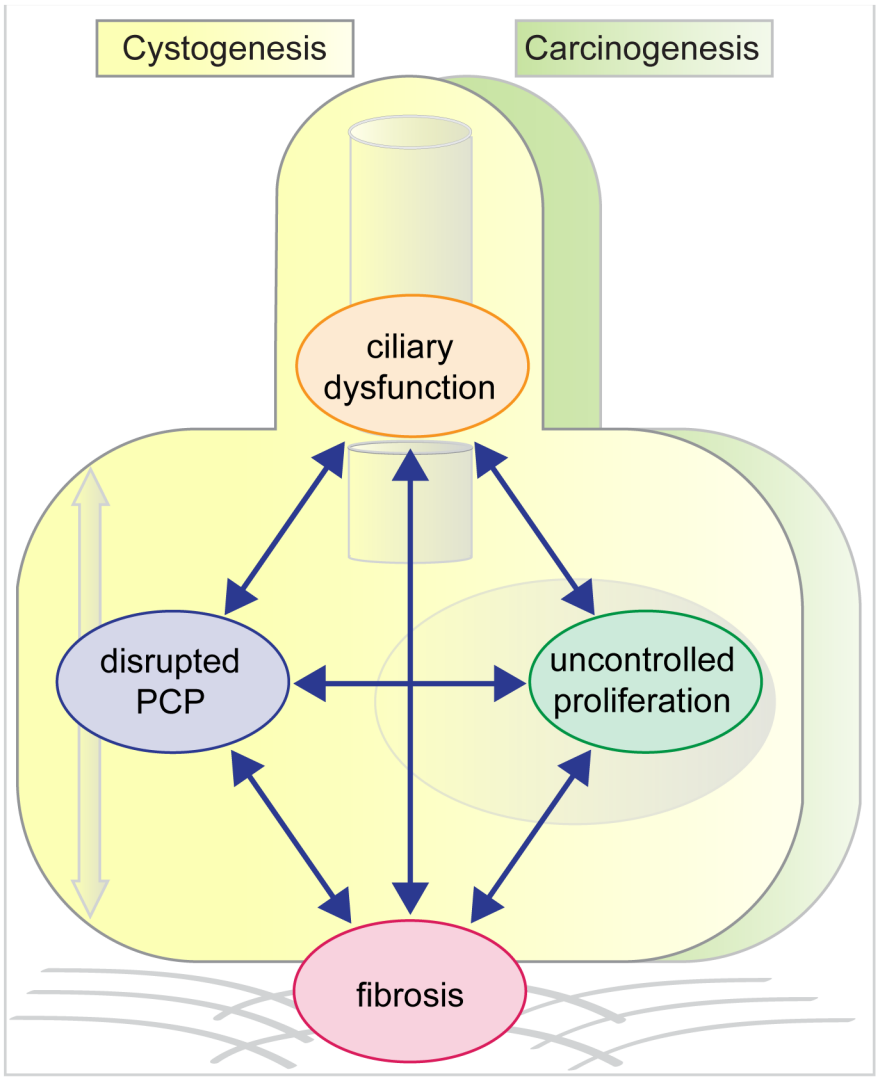

Figure 4. Interconnection of cystogenesis and carcinogenesis

Ciliary dysfunction, abnormal proliferation, disrupted planar cell polarity (PCP) and fibrosis interplay in the pathogenesis of PKD and cancer.