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Ciliary signaling in cancer

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Abstract

Although tumors initiate from oncogenic changes in a cancer cell, subsequent tumor progression and therapeutic response depend on interactions between the cancer cells and the tumor microenvironment (TME). The primary monocilium, or cilium, provides a spatially localized platform for signaling by Hedgehog, Notch, Wnt, some receptor tyrosine kinases (RTKs), and mechanosensation. Changes in ciliation of cancer cells and/or cells of the TME during tumor development enforce asymmetric intercellular signaling in the TME. Growing evidence indicates that some oncogenic signaling pathways as well as some targeted anti-cancer therapies induce, while others repress, ciliation. The links between the genomic profile of cancer cells, drug treatment, and ciliary signaling in the TME likely affect tumor growth and therapeutic response.

[H1] Introduction

In solid tumors, initiation, progression, and therapeutic response are strongly influenced by paracellular signaling between cancer cells and cells in the tumor microenvironment (TME), such as immune cells, endothelial cells and their precursors, and fibroblasts. This signaling provides resistance to environmental stresses or cancer therapies that induce cell death, and supports invasion and metastasis.

The primary monocilium, expressed on almost all non-hematological cell types in the body, is emerging as a mediator of paracellular signals that control cancer growth and therapeutic responses. Vertebrate monocilia, typically referred to as primary cilia, have structural features in common with the motile flagella of simple eukaryotes such as *Chlamydomonas*, and have been studied for over 60 years. Cilia protrude from the cell surface into the

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extracellular space, and function as spatially restricted hubs, displaying receptors through which cues from soluble ligands, or from ligands tethered to the extracellular matrix (ECM) can be received. Although cilia play important roles in tissue patterning in development, and inherited mutations affecting core ciliary components lead to a group of syndromes known as ciliopathies¹ (Box 1), until recently, the role of cilia in cancer has not been generally appreciated.

In the past decade, accumulating data has established direct links between 1) signaling processes mediated through ciliary receptors, 2) signaling processes that regulate ciliary formation and function, and 3) signaling processes that regulate tumor growth and response to treatment. These links impact core cancer signaling pathways including the Hedgehog, WNT and PDGF cascades, the proteasome, mitotic regulatory kinases, and DNA damage response. In this Opinion, we will highlight important new findings about the role of cilia in cancer, and suggest directions for future research.

[H1] Essential properties of cilia

Our current understanding of mammalian cilia is to a large extent based on insights from foundational research into the flagellum in the green algae *Chlamydomonas*²⁻⁷, the description of which is beyond the scope of this review. We also note, biology of the primary moncilium differs in some important regards from that in specialized multiciliated cells (Box 2), which we will not cover here.

Primary cilia localize to the surface of the majority of cells in most adult vertebrate cell types (with the notable exception of hematopoietic cells). The ciliary structure is a compartmentalized membrane encompassing a microtubule-based core (the axoneme) anchored by the basal body (a modified centriolar structure that has undergone prior mitotic division) (Figure 1). Structures associated with a transition zone located near the base of the cilium, including a ciliary gate, help maintain higher concentration of specific proteins and lipids in cilia (⁸, and references therein).

[H2] Ciliary protrusion-resorption cycles, length control, and cell cycle.

The formation of the primary cilium is directly linked to control of the cell cycle⁹⁻¹³ and occurs post-mitotically, in the G0 or early G1 phase, beginning with axoneme protrusion from the basal body. The cilium typically (although not invariably) persists through G1 but is resorbed before cells enter mitosis (Figure 2). The timing of resorption differs between different cell lineages, most commonly occurring in S or G2 phase. Following resorption, the centriole is released from the former ciliary basal body, and undergoes a differentiation process to serve as a microtubule organizing center (MTOC) and support mitosis. When the cells become quiescent, the basal body migrates back to the membrane and cilium formation recommences. The protrusion and resorption processes, and the trafficking of some ciliary signaling proteins, depend on regulation of the intraflagellar transport (IFT) machinery (Figure 1) which is supported by action of the BBSome complex, the Meckel syndrome (MKS) and nephronophthisis (NPHP) complexes, and other proteins^{14,15}.

Definition of the signaling cues governing the physical machinery for assembly and disassembly has been a topic of great interest (Figure 2; reviewed in^{11,13,16,17}). Aurora-A kinase (AURKA), Polo-like kinase 1 (PLK1), and NIMA-related kinases (NEK or NRK), which are regulators of the cell cycle, have emerged as crucial regulators of cilia disassembly. Suggestively altered expression and/or activity of some of these proteins is directly linked to cell transformation^{18,19}. In addition to controlling protrusion and resorption, some of these signaling pathways modulate *ciliary* length¹⁷, an important rheostat for cilia-based signaling receptors.

[H1] Signaling influenced by ciliation

Several signaling pathways important for paracellular communication between cancer cells and cells in the TME have been associated with the primary cilium, of which Hedgehog (Hh), Notch, Wnt, and platelet-derived growth factor (PDGF) signaling are some of the best characterized (Figure 3)^{20,21}. Because this field is only emerging, for some of these ciliary signaling pathways, their relevance to tumor pathogenesis has only been explored in a limited number of tumor types: however, relevance has been demonstrated for all systems noted below in at least some tumor types.

[H2] Hedgehog.

The Hh signaling system²² (Fig 3A) promotes tumour growth by serving as oncogenic driver conditioning the TME in several tumor types. The three Hh family members in mammals include Sonic (SHH), Indian Hedgehog (IHH), and Desert Hedgehog (DHH), SHH has been most studied. Hh proteins are secreted by epithelial or tumor cells, and bind to the Patched (PTCH1) receptor, which is localized to the ciliary membrane of either the Hh-secreting cell, or neighboring cells, which can be either additional epithelial/tumor cells, or non-transformed stromal cells. In the absence of HH binding, PTCH1 provides repressive signals that sequester a second protein, Smoothened (SMO) in intracellular vesicles outside the cilium²³. Hh binding to PTCH1 causes PTCH1 to be trafficked out of cilia, allowing SMO to translocate into the cilia where it activates a transcriptional program dependent on GLI effectors²⁴. Additional cellular proteins can modulate this signaling: for example, GPR161 has recently been defined as a Hh regulator with cancer relevance (see Table S1). Activated GLI proteins move to the nucleus, where they bind and transcribe a suite of genes that control processes relevant to tumor growth and treatment resistance, including proliferation (CCND1, MYC), epithelial-mesenchymal transition (EMT) (SNAIL), survival (BCL2), stem cell identity (SOX2, NANOG), and angiogenesis (ANG1 and 2).

[H2] Notch.

The transmembrane Notch proteins (Notch1–3) regulate cell fate determination and tissue homeostasis (Fig 3B). In cancer, abnormal activation of Notch proteins in lung, breast, and other tumor types enhances stem cell characteristics, promotes invasion and metastasis, and supports angiogenesis, in part via interactions with ERBB2 and VEGF signaling cascades^{25,26}. Notch pathway activation (for example, in embryonal development) requires cleavage of ligand-bound, activated Notch by the -secretase complex, localized proximal to the basal body, leading to release of the Notch intracellular domain (NICD). The cleaved

NICD translocates to the nucleus as part of the CSL transcription factor complex, and induces MYC, CCND3, HES1 and other genes. A study of skin development has shown that knockdown of IFT transport proteins causes defects in Notch signaling and impairs progenitor cell differentiation²⁷. Further, during epidermal and neural differentiation, Notch signaling primes progenitor cells to respond to SHH, by lengthening cilia, and regulating localization of SMO and PTCH1 at cilia^{27–29}.

[H2] WNT.

A large group of secreted WNT ligands influence the balance between cellular differentiation, polarity controls, and proliferation to regulate tissue homeostasis³⁰. Altered WNT signaling (Fig 3C) contributes to the loss of cell polarity associated with increased proliferation in numerous epithelial cancers (e.g. ³¹. Canonical WNT signaling depends on activation of a β -catenin effector. Non-canonical WNT signaling involves regulation of planar cell polarity (PCP) effectors, and proteins such as phospholipase C (PLC), that regulate calcium responses³⁰. Importantly, in studies of embryonal development performed in multiple vertebrate species and cell types, primary cilia have been reported to act as switch between canonical and non-canonical Wnt signaling, which induce distinct sets of genes influencing cell polarity and cell growth, and disruption of ciliogenesis caused by mutations affecting ciliary transport restricts the canonical WNT pathway^{32,33} (although at least one study of embryonal development has challenged these findings, implying cell type specificity³⁴). Studies in numerous vertebrate cell types, and in zebrafish and Xenopus development, have indicated that the ciliary protein inversin/NPHP2 regulates the expression and localization of the key WNT effector Dishevelled (DVL1), targeting it for degradation and thereby controlling pathway outputs³³. Based on studies in transgenic mice, zebrafish embryos, and human cell lines aimed at gaining insight into normal development and differentiation, BBS proteins interact genetically with proteins essential for PCP signaling, and BBS mutations share phenotypes with PCP mutations³⁵. Subsequently, in zebrafish embryos *wnt11* and *wnt5b* were shown to functionally interact with *bbs1*, *bbs4* and *mkks* / *bbs6*, and depletion of these BBS/MKS proteins reduced degradation and increased Wnt signaling through a β -catenin canonical effector³⁶.

[H2] Receptor Tyrosine Kinases and other membrane associated kinases.

Elevated expression or activity of receptor tyrosine kinases (RTKs) is one of the most common oncogenic driver mechanisms. While RTKs are typically thought of as acting from microdomains on the plasma membrane, a growing body of work demonstrates that ciliary pools of RTKs exist and may have specialized regulatory function. One of the earliest examples of a ciliary RTK was the demonstration that the PDGFR α receptor localized to primary cilia in mammalian fibroblasts (Fig 3D), that the cilia was required for fibroblasts to respond to the PDGF-AA ligand, and that PDGF-AA activated Mek1/2 specifically at the basal body, resulting in transcription of cancer-relevant pro-proliferative genes including STATs, c-Fos, and c-Jun³⁷. Unciliated fibroblasts are unable to respond to PDGFR α -dependent chemotaxis signals^{38–40}, and have elevated signaling of the cancer-relevant RTK effector mTOR⁴¹. PDGFR α is expressed on cilia on numerous cell types, including fibroblasts, ovarian surface epithelial (OSE) cells, neuroblasts, and others⁴².

Various studies have shown that cancer-relevant RTKs including insulin-like growth factor 1 receptor (IGF1R), epidermal growth factor receptor (EGFR), angiopoietin receptor (Tie1/2), fibroblast growth factor receptor (FGFR), and *recepteur d'origine nantaïs* (RON) are located within or proximal to primary cilia in non-malignant cells of various tissues⁴². For some of these RTKs, differences in activation capacity based on ciliary localization have been reported: for instance, in adipocyte differentiation, ciliary IGF1R is more sensitive to insulin than receptor found on the plasma membrane⁴³.

In addition to RTKs, function of the serine-threonine kinase transforming growth factor β (TGF β), an important mediator of epithelial-mesenchymal transition (EMT), has been linked to the primary cilium in some cell types, such as human and murine fibroblasts. Cell surface expression of TGF β is regulated in part by clathrin-dependent endocytosis (CDE), a process organized at the ciliary pocket, and there is evidence for a localized pool of cilia-associated TGF β receptors, with genetic loss of cilia reducing TGF β -mediated signaling in some systems, such as human fibroblasts⁴⁴.

[H2] Other ciliary signaling systems.

Cilia are also involved in transmitting cues through mechanosensation, directly through interactions with tethered structures, or indirectly through bending induced by nodal flow, shear stress forces, or changes in osmolarity in cilia interacting with fluids in luminal space.

In development and in tumors, growth of cilia-expressing cells is conditioned by the mechanical stiffness of the microenvironment, which reflects the composition of ECM produced both by the ciliated cell and stroma⁴⁵. Part of this response reflects physical changes in the ECM architecture: for example, one study showed that growing human mesenchymal stem cells on micropatterned grooves was sufficient to lengthen cilia and alter WNT/ β -catenin signaling, in a process dependent on reorganization of intracellular actin-myosin signaling⁴⁶. Integrins and NG2 proteoglycans displayed on cilia in murine chondrocytes mediate interactions with fibronectin and other specific ECM component proteins, with integrin activity regulating a cell attachment signaling cascade through interactions with the integrin effectors SRC and FAK, and the triggering of calcium signaling^{47,48}. Defects in this signaling process can lead to fibrosis, a common element in the tumor microenvironment that promotes cancer progression⁴⁵.

A growing number of G-protein coupled receptors (GPCRs) have been found to localize to the cilia on many types of human cells⁴⁹. Importantly, these GPCRs include receptors for a wide variety of signals relevant to energy homeostasis. Defects in cilia manifested through dysfunction of these signaling systems have been strongly associated with obesity, a predisposing condition for cancer^{50,51}.

[H1] Ciliation impacts cancer pathogenesis and response to therapy

As discussed below, ciliation is not ubiquitous in all cells in mature adults. This fact, coupled with the fact that cilia undergo resorption-protrusion cycles linked to cell cycle and external stressors, has important consequences for the role of these organelles in the context of cancer and cancer-directed therapies. A minimal implication of this cycling process is that

cellular capacity to respond to ligands for, or drugs targeting, ciliary receptors is heterogeneous across organ systems and cell types. An intriguing implication is that a subset of oncogenic drivers, through under-appreciated effects on control of ciliation, may lead to complex, cell type-specific responses to therapies targeting signaling systems with a ciliary component. A growing body of evidence supports these possibilities.

[H2] Cell lineage and transformation-dependent ciliation

From the earliest stages of embryogenesis, lineage-specific differences in cell ciliation result in functional differences in response to Hedgehog and other cues⁵². In mature organisms, ciliation differences persist in distinct tissues, and oncogenic transformation influences ciliation status in distinct ways.

For example, although *lymphoid* cells utilize some components of the IFT machinery in formation of the immune synapse, these cells lack cilia^{53,54}. In contrast, in mouse *mammary tissue* cilia are present on luminal epithelial, myoepithelial, and stromal cells during branching morphogenesis in development, but subsequently are lost from cells of the luminal epithelia. Mutations in IFT proteins compromise mammary branching which is linked to increased canonical Wnt and decreased Hh signaling⁵⁵, and likely reflects defects in paracellular signaling from SHH-expressing luminal cells to ciliated basal cells⁵⁶. In humans, the percentage of ciliated mammary cells is reduced early in tumor formation, in premalignant lesions, and in invasive breast cancers^{57,58}. This is associated with low expression of ciliary structural proteins, including those which are required for the IFT and BBSome complexes⁵⁸. Ciliation is also reduced, although to a lesser extent, in the surrounding stromal cells associated with both premalignant and invasive cancers. Inhibition of ciliogenesis in the polyoma middle T (PyMT) mouse model of breast cancer by deletion of *Ift88* in the tumor cells caused earlier tumor formation, faster tumor growth, higher grade tumors, and increased metastasis⁵⁹, coupled with elevated Hh pathway activity.

As another example, in the *pancreas*, cancer formation commonly goes through set stages in which ductal acini typically convert through pancreatic intraepithelial neoplasia precursor stages (PanIN stages 1–3) to overt pancreatic ductal adenocarcinomas (PDACs). Although normal pancreatic ductal epithelia, islet cells, and centroacinar cells, are highly ciliated, cilia are sharply reduced during formation of PDACs, from the earliest precursor stages⁶⁰, and in cases of the pre-neoplastic condition of pancreatitis⁶¹. Human PDACs have high levels of intratumoural heterogeneity, with some cancer cells more differentiated and some less so; a study of clinical outcomes showed that residual ciliation of cancer cells segregated to the well-differentiated areas (Figure 4A), and a higher level of cancer cell ciliation was prognostic of improved overall survival⁶². In mouse models, induced loss of ciliation by deletion of IFT components (*Ift88* and *Kif3a*) in the pancreatic epithelium, or constitutive loss of these components, caused abnormalities including ductal metaplasia and dilation, fibrosis, abnormal ductal morphology, and lipomatosis^{63,64}. Similarly, cancer cell ciliary loss in *prostate* cancer is associated with elevated Wnt/ -catenin activity, loss of tissue homeostasis and increased malignant characteristics⁶⁵; in *ovarian* cancer, associated with defects in Hh and PDGFR α signaling⁶⁶; and is similarly associated with aggressive tumor growth in *chondrosarcomas*⁶⁷, and in other cancer types⁶⁸.

Importantly, some cancers depend on retention rather than loss of ciliation. Two well-studied counter-examples are *medulloblastoma* (Figure 4B) and *basal cell carcinoma* (BCC), both of which depend on activation of the Hh signaling pathway within cancer cells. Intriguingly, although constitutive Hh signaling is required in these tumors, this can be achieved either through mutational activation of ciliary proteins that act upstream in the cascade, such as SMO or PTCH1, or downstream, such as GLI2. Primary cilia have a tumour-promoting effect in medulloblastoma and BCC if the tumour-inducing event is oncogenic mutation of *Smo*, but have a tumour-inhibitory effect if the tumour-inducing event is mutational activation of *Gli2*, as first shown in mice ^{69,70}. These seemingly paradoxical effects are consistent with a role for cilia as a platform for both the activation and the repression of the Hh signaling pathway⁷⁰. Here, activation of Hh signalling is mediated through SMO-dependent induction of PKA phosphorylation of GLI2, which switches GLI2 from a repressive to an active form, leading to induction of target gene transcription ^{70,71}. Hence, if *Ptch1* or *Smo* are mutationally activated, cilia are required for transmission of downstream signaling. However, when Gli2 is mutationally activated, reducing the number of cilia by genetic deletion of *Kif3a*, which is required for cilia assembly, does not affect skin tumourigenesis⁷⁰.

[H2] Ciliation in the tumor microenvironment.

Among the cells of the TME, infiltrating lymphocytes and myeloid cells are non-ciliated, whereas other cells of the TME, such as fibroblasts and endothelial cells are more likely to be ciliated than cancer cells (Figure 4 A, B). Because many important signaling systems are located to cilia, this asymmetry between cancer and non-cancer cells impacts paracellular signaling in the TME.

Enhanced SHH secretion by cancer cells in pancreatic cancers and other cancers of the digestive tract, including esophageal, stomach, and biliary tract (but excluding colorectal), is required for tumour growth ^{72,73}. In pancreatic cancer, SHH in conjunction with other factors (such as TGF) induces the recipient pancreatic stellate cells in the TME to undergo a desmoplastic reaction that in turn drives aggressive phenotypes⁷⁴. An extensive proteomic analysis dissecting this interaction demonstrated that PDAC secretion of SHH caused recipient pancreatic stellate cells to transcribe a suite of genes required for desmoplastic ECM production, and to excrete the growth factors IGF1 and GAS6. These growth factors reciprocally stimulated IGF1R/IRS1 and AXL/TYRO3 receptors on PDAC cancer cells, supporting the activation of over 90% of the measurable cancer cell phosphoproteome⁷⁵. This result implied profound importance of receipt of SHH signals by the cilia in stromal reciprocity in PDAC. In other cancers, examples of potent roles for SHH and cilia-mediated stromal reciprocity include breast cancer, where an epithelial Hh/stromal GLI1 signature predicted poor survival and increased metastasis⁷⁶. SHH conditioning of stromal cells contributes to prostate cancer growth⁷⁷; IHH secreted by Apc-mutated colonic epithelia conditions gut stroma to support adenoma formation and growth ⁷⁸. This appears to be a common mechanism for activating the TME.

[H2] Oncogenic signaling can cause loss and/or shortening of cilia.

As noted above, the regulation of the primary cilium is closely associated with cell cycle, with greatest prevalence of the structure in quiescent post-mitotic cells, and most consistent loss prior to mitosis^{15,68}. Over the past several decades, a question of high interest in the field of ciliary biology has been whether cilia *qua* cilia have an active role in restricting cell cycle re-entry, and whether the structure intrinsically functions as a tumor suppressor. Although this topic has been much discussed, it has been difficult to resolve, as many proteins originally thought to be cilia-specific have emerged as having additional non-ciliary functions. However, evidence exists for defined driver oncogenes or transformation-associated processes that target cell cycle also directly affecting ciliation.

The Aurora-A (AURKA)/STK15 serine threonine kinase, most studied for its activity in mitosis, was first identified as an oncogenic driver of transformation and genomic instability for breast tumours, and subsequently shown to act as an oncogene in many other tumor types¹⁸. Building on work in *Chlamydomonas*⁷⁹, transient activation of AURKA prior to resorption of ciliation was found to occur not only at the G2/M transition point, where AURKA activity was well documented, but also in quiescent G0/G1 cells, in a pool of AURKA localized to the ciliary basal body. Such AURKA activation is a necessary and sufficient, proximal driver of ciliary resorption for humans and other vertebrates, in both cancer and untransformed cell types^{68,80}. AURKA activation requires interaction with a number of partner proteins; at least some of these proteins, such as NEDD9/HEF1, were shown to be required for ciliary resorption⁸¹, and also are oncogenically overexpressed in a significant number of tumor types in mice and humans⁸². Conversely, interactions of the tumor suppressor VHL and glycogen synthase 3-beta (GSK3) are essential for ciliary maintenance. Loss of these proteins in mammalian kidney cells causes rapid ciliary loss, in part because *VHL* inactivation stabilizes the transcription factors HIF1/2⁸³ and -catenin, inducing AURKA and NEDD9/HEF1. Given the near ubiquity of VHL suppression in renal cell carcinomas (RCCs, a type of tumor that like many others is characterized by reduced ciliation), AURKA is active in this disease⁸⁴. In contrast, induction of the histone deacetylase HDAC2 contributes to elevated AURKA activity and loss of cilia in PDACs⁸⁵.

Oncogenes that stimulate continuous proliferation, and prevent cells from entering quiescence, also decrease ciliation as an indirect consequence of the cells not entering a quiescent state. Oncogenically activated KRAS actively suppresses the program of ciliary formation, through a process that is poorly defined, but reversible *in vitro* by inhibition of the KRAS effector PI3K⁶⁰. This potent activity of RAS, coupled with the common nature of RAS mutations in many tumors, is likely to contribute to common loss of ciliation.

RAS is a central downstream effector of numerous RTKs, including EGFR, PDGFR, FGFR, and others which are commonly amplified or have activating mutations in tumors. Some of the earliest studies of molecular controls of ciliary resorption-protrusion cycles focused on the fact that ciliary protrusion required growth of cells under conditions of low or no serum, while serum induced rapid resorption. The first serum factor shown to specifically induce ciliary resorption was PDGF⁸⁶; EGF, IGF, and FGF also contribute to resorption⁸⁷. Overexpression and/or constitutive activation based on mutation of the RTKs for these growth factors would be expected to decrease ciliation. For example, activation of epidermal

growth factor receptor (EGFR) kinase has been shown to suppress ciliogenesis in retinal pigmented epithelial cells⁸⁸. It is also important to note that some of these receptors promote ciliary resorption even though they are not located at cilia (e.g. PDGFR β ⁸⁹).

Suggestively, genomic data of cilia-dependent medulloblastoma and BCC cancer cells shows a paucity of genetic changes involving activated or overexpressed *AURKA*, *VHL*, *RAS*, or RTK genes. For example, in 46 medulloblastoma cases reported in TCGA⁹⁰, and an additional 125 cases in an independent study⁹¹, there are no mutations affecting *VHL*, *RAS*, or RTK genes. In 293 specimens of BCC⁹², mutations affecting *PTCH1* (in 74% of cases), *SMO* (in 20% of cases), *SUFU* (in 8% of cases), *NOTCH1* (in 29% of cases), and *NOTCH2* (in 26% of cases) were common, but no mutations or amplifications affecting *RAS*, *VHL*, or *AURKA* were observed, with only 2% of cases having mutations in the RTK *ERBB2*.

Nutrient limitation in rapidly growing tumors often triggers the pro-survival process of autophagy, involving the destruction and recycling of damaged proteins. Several studies have shown that activation of autophagy influences ciliogenesis⁹³. Studies in the human breast cancer cell line MCF7 as well as non-malignant murine and human cell models, indicated that induction of autophagy is associated with ciliary protrusion and lengthening, whereas inhibition of autophagy results in cilia shortening and loss^{94,95}. Reciprocally, based on studies in multiple murine cell types, cilia-based signals from Hh or other factors can activate proteins trafficked to the basal body by the IFT apparatus, with IFT-deficient cells having a reduced level of autophagy⁹⁶.

In cancer cells, specific oncogenic signals, rapid cell cycle, and increased autophagy stimulate proteasomal activity. There are extensive connections between ciliation status, the ciliary transport machinery, and regulation of the proteasome in normal and transformed cells (reviewed recently by⁹⁷). For example, studies in human primary cultures, murine tissues and zebrafish models indicate that ciliary proteins including BBS4 and OFD1 directly interact with subunits of the proteasome, supporting expression and activity of the proteasome at the ciliary base, and regulate the cancer-relevant NF- κ B pathway⁹⁸. Also, proteasomal regulation of the ciliary protein trichoplein, an *AURKA* inhibitor, influences ciliation in human retinal pigmented epithelium cells and other cell models⁹⁹, as well as the ability of cells to respond to signals emanating from ciliary receptors.

[H2] Ciliary proteins affect cancer initiation and progression.

Although there has been little prior organized effort to connect changes in ciliation *per se* to cancer, a growing number of studies indicate a role of genes with roles in control of ciliary structure or function in carcinogenesis. Although whether the function of the respective genes in cilia is connected or independent from their role in cancer has in general not yet been established, the number of examples suggests a direct link which deserves further investigation. For example, split ends (SPEN), an estrogen receptor α co-repressor, is coexpressed with a suite of ciliary genes, and supports ciliary biogenesis. Based on siRNA depletion experiments, SPEN promotes migration in the ciliated, immortalized but not transformed MCF-10A cell line, and in ciliated, but not unciliated, human breast cancer cells; in addition, studies of patients with breast cancer found a correlation between early metastasis and high expression levels of SPEN in two independent cohorts of 77 (HR 2.25, P

= 0.03) and 170 (HR 2.23, $P = 0.004$) patients. Interestingly, the correlation was observed in hormone receptor (HR)-negative patients, which have some ciliation, but not HR-positive breast cancer, which typically lack primary cilia¹⁰⁰.

NEK2 interacts with KIF24 to regulate cilia disassembly during cell cycle. NEK2 was highly overexpressed (5–30-fold) in all members of a panel of breast cancer cell lines of various subtypes in comparison to normal human mammary epithelial cells. Depletion of NEK2 increased ciliation and supported proliferation in breast cancer cells that lack cilia, including the triple negative Hs578T cell line model; function-testing experiments indicated that interactions between NEK2 and KIF24 were required for these activities¹⁰¹.

Knockdown of the tubulin glycine ligase TTLL3, which modifies the ciliary axoneme, reduced the number of primary cilia and increased the proliferation of colon epithelial cells, strongly promoting development of colorectal carcinomas (CRCs) in a mouse model. Decreased levels of TTLL3 was associated with progression of human CRC¹⁰².

A mouse model of SHH-dependent medulloblastoma dependent on constitutively active SMO depended on expression of inositol phosphatase INPP5E for proliferation, tumor progression, and SHH signaling. In this model, INPP5E regulates a cilia-compartmentalized $\text{PtdIns}(3,4,5)\text{P}_3/\text{AKT}/\text{GSK}3\beta$ signaling axis to maintain tumor cell cilia. Interestingly, in a subset of human medulloblastomas, low INPP5E mRNA levels were associated with increased overall survival¹⁰³.

The PCP effector Inturned (INTU) is overexpressed in human basal cell carcinoma (BCC), with increased INTU expression correlating with elevated formation of primary cilia, and Hh pathway activity. Based on in vitro and in vivo experiments using a mouse model, INTU essential for formation of primary cilia and Hh signaling in BCC, based on a role that includes promoting IFT complex A assembly¹⁰⁴.

Experiments in two in vitro cell lines used as models for cell polarity controls (MDCK and the moderately ciliated LNCaP prostate cancer cell line), supplemented by analysis of tissue development in *Xenopus*, demonstrated that hyperactivation of the lipogenic transcription factor sterol regulatory element binding protein 1c (SREBP1c), associated with the abnormal activation of fatty acid synthesis pathways in many cancers, disrupted cilium formation and caused ciliary defects in environmental sensing, associated with distortion of polarized tissue structure. Conversely, blockade of an SREBP1c-activating cleavage increased LNCaP cell ciliation 5-fold¹⁰⁵. The polarization defect seen with SREBP1c overexpression likely reflects the ciliary defect, given other related findings linking ciliation status and integrity of polarized epithelial sheets¹⁰⁶ and the dense connections mapped out between IFT proteins and a CPLANE (ciliogenesis and planar polarity effector) complex¹⁰⁷.

Links between DNA damage response (DDR) and ciliary proteins are emerging¹⁰⁸. For example, studies in two standard cell line models of ciliation (human RPE1 cells and mouse Inner Medullary Collecting Duct (IMCD3) cells), and a zebrafish in vivo model, have shown mutation or loss of the centrosomal protein CEP164 causes defects of ciliogenesis concomitant with defects in DDR, and also EMT, and changes in rate of apoptosis¹⁰⁹. NEK8/NPHP9, mutated in the ciliopathy nephronophthisis, was identified as a critical

component of the DDR linked to replication stress based on work using several human cancer cell lines, and IMCD3 cells¹¹⁰.

8.7% of families with evidence for inherited testicular germ cell tumors (TGCT) bear damaging mutations in cilia-microtubule genes (CMGs). Of these, disruption of dynein axonemal assembly factor 1 (DNAAF1) predominantly localized to the cilia although found also at the spindle poles in some cell lines, and implicated in primary cell dyskinesia (PCD) of motile cilia and in male infertility, was one of the most significantly mutated. Some of the other genes noted included DYNC2H1 and DRC1 (both localized to the tubulin cytoskeleton and ciliary axoneme), and CEP290 (more broadly localized to cytoskeleton, microtubule organizing center, centrosome, and basal body)¹¹¹.

Transcription factors known to induce proteins involved in ciliary formation (including the RFX factors and FOXJ1) are increasingly linked to roles in tumor formation and prognosis¹¹². Whether these functions are linked or independent is a current topic of investigation.

An extensive study comparing patterns of mutation in spontaneous human RCC versus a murine RCC arising from triple mutation of *Vhl*, *Tp53*, and *Rb1*, showed similar enrichment for disruption of ciliary genes: 40% of human tumors analyzed contained one or more such mutations¹¹³.

Due to space limitations, this is an incomplete list of recent, in depth cilia-cancer studies, in a rapidly growing field. In addition to those discussed above, high throughput screens and database analyses have suggested further cilia-associated genes relevant to cancer biology (Supplemental Table 1).

[H1] Drug-cilia interactions.

The oncogenic pathways described in the preceding section include some of the most studied and most “druggable” pathways in cancer therapy. Until recently, given the prevailing view that cilia were mostly relevant to ciliopathies and developmental signaling, little work explicitly addressed the hypothesis that some or many cancer drugs may be targeting cilia, and that activity of these drugs on cilia in the cancer cell or cells in the TME may influence signaling responses in potentially unpredictable ways. However, a growing number of publications support the idea that drug-cilia interactions in cancer are not uncommon (Table 1).

Some of the earliest studies of flagella and cilia probed regulation of the protrusion-resorption cycle with taxanes and vinca alkaloids, agents that provide the basis for common chemotherapies. Given the importance of regulated IFT on a dynamic microtubule-based axoneme for this cycle, in experiments performed in diverse models including mammalian cell lines, and vertebrate and invertebrate organisms, not surprisingly some of these agents had potent effects, with the microtubule-destabilizing agents vinblastine and colcemid blocking ciliary formation^{114–116}, and taxol inducing elongated, morphologically abnormal cilia¹¹⁷. More recently, the role of cytoskeletal proteins and modifications in controlling the

ciliary cycle and ciliary length has been probed by several groups, revealing dependence on actin, tubulin, and associated proteins¹¹⁸.

Among targeted agents, alisertib is a selective AURKA inhibitor, under clinical development for relapsed/refractory peripheral T-cell lymphoma and other indications¹¹⁹. Alisertib⁸¹ and a chemically distinct Aurora-kinase inhibitor, PHA-680632⁸⁰, completely block ciliary disassembly in normal and immortalized mammalian cells, *in vitro* and *in vivo*. However, although cilia are constitutively retained in cells treated with alisertib, the drug may partially disrupt ciliary signaling, based on observed ciliary morphological abnormalities, and a trafficking defect in the ciliary protein adenylyl cyclase 6 (ADCYC6) in alisertib-treated cells⁸¹.

PLK1 function is linked to that of AURKA and activated PLK1 also induces rapid loss of ciliation^{120,121}. Because PLK1, like AURKA, is important for entry into mitosis, targeted agents such as volasertib are also in clinical trials¹²². The activity of these agents in regulation of cilia has never been assessed. However we can speculate that at least one such agent, rigosertib, described as a dual PLK1/PI3K inhibitor, might potentially be potent in stabilizing cilia, given the reports of PI3K being essential for KRAS-induced deciliation⁶⁰, and deciliation induced by an INPP5E mutation^{87,123}.

RTK inhibitors are some of the most common targeted inhibitors in cancer treatment. Given the role of EGF, PDGF, FGF, and other ligands for RTKs in promoting ciliary resorption, small molecule and potentially antibody inhibitors of these RTKs would be expected to promote greater levels of ciliation. Of the limited data available, inhibition of PDGFR with a neutralizing antibody, or treatment with the PI3K inhibitor Ly294002, promoted ciliary stability, in experiments using mouse embryo fibroblasts (MEFs) and an *in vivo* mouse model with wild type or null INPP5E⁸⁷. A screen of drugs to identify agents able to restore cilia to PDAC cells identified the EGFR inhibitor gefitinib, and sirolimus (rapamycin), an inhibitor of the EGFR/RAS effector mTOR, with results confirmed in multiple human cancer cell lines (representing pancreatic, kidney, breast, and lung cancers)¹²⁴.

Heat shock protein 90 (HSP90) is a chaperone for a number of oncogenic proteins, and several HSP90 inhibitors have advanced to the clinic based on the addiction of tumors to oncogenes dependent on HSP90¹²⁵. The HSP90 inhibitor ganetespib causes rapid and sustained ciliary loss in murine and human cell types, *in vivo* and *in vitro*, through a mechanism involving reduction in proteasomal function, and stimulation of AURKA, with HSP90-dependent deciliation blocked by alisertib¹²⁶.

It is important to remember that cancer patients are typically in late middle age or elderly, and often have comorbidities including hypertension, diabetes, obesity, and/or cardiovascular disorders¹²⁷. In addition, cancer patients are likely to experience anxiety or depression, either as a pre-existing condition or related to their cancer diagnosis¹²⁸. Treatments for some of these additional pathological conditions are already known to affect cancer progression¹²⁹. Hence, comorbidity is worth considering in the context of a discussion of ciliation and cancer, as some of the signaling systems associated with these disorders involve ciliary-localized receptors, and some of the drugs in clinical development

or use to treat comorbidities are known or likely to influence ciliation in some systems. Relevant examples of cilia-affecting drugs include the GPCR MCHR1, with preclinical compounds in development for treatment of obesity and depression¹³⁰; drugs targeting the dopamine receptor system, including reserpine, in use for hypertension^{131–133}; and some benzodiazepines, in use for anxiety¹³⁴. Potential interaction of such agents with cilia in the tumor microenvironment is essentially a black box.

An elegant recent study provides evidence for the therapeutic relevance of tumor modulation of ciliation as a cause of drug resistance in some cancer settings. Drugs targeting SMO have been developed as a means of inhibiting SHH signaling, with sonidegib/LDE225¹³⁵, saridegib/IPI-926¹³⁶, and vismodegib/GDC-0449¹³⁷ assessed in preclinical and clinical trials for BCC, medulloblastoma, and other cancers¹³⁸. As predicted, SMO-targeted inhibitors are active in medulloblastomas dependent on mutations in PTCH1 that require ciliary signaling, but not in those associated with downstream activating mutations¹³⁹. Inhibition of Hh is also productive in BCC, where Hh inhibitory agents are advancing in the clinic¹³⁷. In a transposon screen to identify genes which are important for resistance of *Ptch* $-/-$ medulloblastoma cells to SMO inhibitors, it was shown that, following treatment with sonidegib, mutations in ciliogenesis genes, including *Odf1* and others, reprogrammed cells to a low level “persister” state, which served as a reservoir for future aggressive outgrowth of resister clones. Importantly, analysis of datasets reporting genomic information for SMO-inhibitor naïve versus treated BCC identified a much higher level of mutations associated with loss of ciliation in treated patients, and a gene signature associated with loss of ciliation¹⁴⁰. These results directly implicate control of ciliation with therapeutic resistance.

[H1] Conclusions.

Understanding and manipulating asymmetric ciliary signaling in cancer cells and cells of the TME can potentially improve understanding of cancer pathogenesis, and application of anti-cancer therapies. For example, the fact that a subset of cancer drugs regulates ciliary dynamics in addition to their primary anticipated mode of action has a number of implications.

First, such drugs may induce unexpected “off-target” effects based on elimination, stabilization, or modification of the ciliary platform for cancer-relevant signaling. Dose scheduling that takes some of these interactions into account may be one way to capitalize on desirable interactions, or minimize undesirable interactions. As a simple example, administration of drugs that stabilize or lengthen cilia should not be co-administered with drugs that inhibit ciliary signaling proteins. Second, drugs affecting ciliary dynamics will act differently in tumors dependent on factors including the degree of ciliation and the dependence on cilia-based signaling in the specific cell lineage from which the cancer cell arises. Drug action will also be influenced by the importance of cancer cell-stromal cell interactions in that tumor type. Third, multiple factors contribute to heterogeneity in solid tumors and complicate efforts to develop personalized treatment strategies, including among others clonal variation, epithelial versus mesenchymal differentiation status, and degree of hypoxia and autophagy. Cancer cells in tumors are likely to include more or less ciliated regions. Fourth, it is likely that more drugs affect ciliation than is currently appreciated. For

example, and although much more work remains to be done in validation and exploration of the underlying mechanism, a recent screen suggests that drugs ranging from antibiotics through hormones to anti-inflammatory agents can induce ciliation, in at least some models¹²⁴.

These issues likely impact therapeutic response. For example, although SMO inhibitors are showing promise in BCC and medulloblastoma, clinical trials to date have shown no efficacy in pancreatic cancer¹⁴¹. At the simplest level, this may reflect inability of the drug to effectively penetrate the tumor mass. However, inhibition of SHH/SMO does not affect the growth of pancreatic cancer cells^{136,142}, due to the deciliation of pancreatic cancer cells with KRAS mutations, leaving potent cell-autonomous pro-growth pathways intact. Indeed, some studies using mouse models indicate that genetic changes inactivating the SHH pathway in fact lead to more aggressive, metastatic cancers by eliminating the tumor-constraining role of the desmoplastic stroma^{143,144}. This might oppose the anti-tumor effects of such an inhibitor in eliminating the ability of SHH-treated fibroblasts to secrete IGF1 and GAS6 (Fig 4B)⁷⁵. Alternatively, the fact that vismodegib was administered in combination with gemcitabine in the trial¹⁴¹ may have impacted its effectiveness, as gemcitabine would potentially influence ciliation by causing transient arrest in S phase, when many cilia had resorbed.

Other preclinical and clinical studies with SMO/SHH inhibitors combine these agents with microtubule modulators, including paclitaxel^{145,146}, and combinations with the depolymerizing agent mebendazole have been proposed^{147,148}. It is hard to predict how these drugs will interact in cancer cells, and in stromal cells: monitoring ciliary expression and functionality would be informative. It is interesting to speculate how a SMO inhibitor would interact with targeted inhibitors of proteins such as PI3K and AURKA, which enhance ciliation (Fig 4B). Furthermore, as mentioned before, ciliary proteins can affect the DDR¹⁰⁸. Therefore, mutations affecting ciliary proteins could modify and amplify the effect of mutations affecting canonical DDR proteins, affecting tumor and stromal response to DNA-damaging therapies.

Among future topics of interest, cilia shed and receive extracellular vesicles (known as ciliary ectosomes); ectosomes secreted from the ciliary tip modulate signaling in other cells¹⁴⁹, and downregulate signaling from cilia¹⁵⁰, with secretion coupled to ciliation¹⁵. The contribution of ciliary ectosomes to cancer is currently a major topic of investigation. Finally, intriguing recent studies raise the possibility that cilia or some of their protein constituents modulate immune system function, and response to cancer immunotherapies. For example, the immunological synapse allows molecular communication between T cells and antigen-presenting cells (APC), which is absolutely essential for antigen recognition and immune response¹⁵¹. Striking similarities exist between the machinery for cilia assembly and formation of the immunological synapse, with both of these processes requiring IFT proteins and centrosomal docking at the plasma membrane; there are even some hints that immune cells harbor the potential to form cilia^{54,152,153}. Defects in IFT-related proteins within immune cells may be expected and in some cases have been shown to impair immune cell maturation and function⁴⁷. Loss of the ciliary protein Kif7 in immature thymocytes resulted in defects in Hh signaling, delayed their maturation to CD8+ cells, and impaired

their interaction with the thymic epithelium in a manner that reduced MHCII expression on the surface of the epithelial cells¹⁵⁴. These intriguing advances, coupled with the rich biology discussed earlier, make it likely that we are only at the dawn of understanding the complex role of ciliation in cancer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Boxes for display.

Inherited defects in ciliary genes lead to ciliopathies.

Integrity of structure and regulation of the primary cilium is essential from the earliest stages of embryogenesis²² for pattern formation and development of many organs. Distribution of cilia is lineage-dependent and stable throughout much of gestation⁵², which specifies the location and types of cells that can respond to ligands with cilia-localized receptors for autocrine, paracrine, and mechanical signals. These include receptors of the Hedgehog (Hh) family proteins, essential for the development of nearly every organ in mammals^{22,155}; the PDGFR receptor, which contributes to skeletal formation and craniofacial development¹⁵⁶, and by polycystins (PKD1 and PKD2), which is essential development of the kidney, and the lymphatic system¹⁵⁷.

Because of these critical functions, inherited mutations in the genes encoding ciliary proteins or signaling proteins with obligate action on cilia result in serious developmental disorders called *ciliopathies*¹. Over 35 different kinds of ciliopathies and 187 established and 241 candidate ciliopathy-associated proteins have been reported¹. Affected organs and processes include the brain (holoprosencephaly, juvenile myoclonic epilepsy, medulloblastoma), heart (congenital heart defects), kidney (nephronophthisis [NPHP], autosomal dominant and autosomal recessive polycystic kidney disease [ADPKD and ARPKD]), liver (liver fibrosis), eyes (Leber congenital amaurosis [LCA], cone-rod dystrophy, retinitis pigmentosa), nose (anosmia, isolated congenital), ears (hearing loss), face (facial anomalies), reproductive system (hypogonadism, genital anomalies, infertility), skeleton (Ellis-van Creveld syndrome, Jeune asphyxiating thoracic dystrophy, orofacioidigital syndrome [OFD], short-rib thoracic dysplasia), energy homeostasis (obesity), and organ placement (situs inversus, heterotaxy). Some syndromes have complex effects on multiple systems (Bardet-Biedl Syndrome (BBS), Cole-Carpenter syndrome, hydroletharus syndrome, Joubert syndrome, Meckel-Gruber syndrome (MKS or MGKS), MORM syndrome, Senior-Løken syndrome), Birt-Hogg-Dubé syndrome (BHD), and others)^{158–160}.

The special case of multiciliated cells.

Specific cell types within vertebrates are multiciliated (~200 to 300 cilia per cell), rather than expressing primary monocilia. Multiciliated cells (MCC) are found in the ventricles of the brain and spinal cord (the ependymal cells), with other MCC in airway epithelia (e.g. nasal, tracheal, lung), and in the fallopian tubes. They differ from monociliated cells in several key features (reviewed in ¹⁶¹). First, these cilia are motile, based on sliding of intraflagellar dynein arms on a 9+2 microtubule structure, with regulated movements vital for movement of fluids or (in the fallopian tube) transit of the ovum. Second, these cells are post-mitotic and terminally differentiated, with multiciliation arising from a regulated over-replication of basal bodies. Third, MCC are similar to monocilia in relying on IFT and BBS proteins for ciliogenesis and function, these cilia typically do not resorb, and formation is regulated by very different cues than in monocilia. It is plausible that defects in multicilia may also contribute to cancer, although by less direct means. As one example, ciliary beating by the multiciliated epithelium provides a first line of defense to cleanse the airways of inhaled debris, pathogens, and other inflammatory stimuli and antigens. Genetic or induced changes affecting length, structure, orientation, percentage of ciliated cells, ciliary beat frequency (CBF) and pattern, and the susceptibility of the cilia to endogenous and exogenous stimuli can contribute to lung disease¹⁶². The most common inherited airway cilia dysfunctions include primary cilia dyskinesia (PCD) and cystic fibrosis (CF), with mutations often lead to defects in cilia or partial structural abnormalities in cilia^{163,164}. Airway cilia functions can also be influenced by environmental stressors such as pneumonia infection, rhinitis and asthma, pollutants, smoking, oxidative stress, and abnormal mucus production¹⁶². Structural or functional abnormalities in airway cilia are hence associated with chronic obstructive pulmonary disease (COPD) and interstitial lung disease, conditions which influence lung cancer risk.

Figure 1. Ciliary Structure.

The axoneme is typically constructed from nine parallel microtubule doublets, protruding from the mother centriole (yellow - also known as basal body) which anchors the primary cilium within the plasma membrane. Y-shaped axoneme-to-membrane connectors, known as the transition zone (TZ) ultrastructure, separate soluble and membrane-associated ciliary proteins from proteins in the cytoplasm and plasma membrane, and function as a 'ciliary gate' limiting the entry of some signaling proteins into cilia¹⁷⁷. This gate depends on actions of proteins from two complexes or signaling modules, known as the Meckel syndrome (MKS) and nephronophthisis (NPHP) modules, to ensure appropriate TZ formation and gate function. For many proteins, transport into and within the cilium depends on active transport by the intraflagellar transport (IFT) machinery; for others entry is by passive diffusion. Protein-bearing vesicles emerging from the Golgi or sorting endosomes are sorted towards the periciliary membrane, and captured by proteins of the IFT machinery. The core elements of the IFT machinery are two sub-complexes, A and B, linked to a BBsome complex bearing cargo. Association of the IFT complexes with Kinesin-2 mediates trafficking to the ciliary tip (anterograde transport), release of protein cargo occurs during progression towards the ciliary tip. At the tip, exchange of motors occurs, with dynein 2 mediating return traffic of the IFT particles and BBsome to the ciliary base (retrograde transport), allowing recycling and ciliary export.

Figure 2. Ciliary assembly and disassembly cycles. Assembly starts when non-dividing cells enter G0/G1 phases and the “mother” centriole differentiates into the basal body, which anchors in the plasma membrane. Interactions between centrosomal protein of 97 kDa (CEP97) and centriolar coiled-coil protein of 110 kDa CP110, which regulate S phase centrosome duplication, suppress new rounds of ciliary assembly¹⁷⁸. PIPKI γ activation promotes tau-tubulin kinase-2 (TTBK2) docking to the basal body, leading to the removal of CP110¹⁷⁹. Ciliogenesis depends on activity of the RAB8 and RAB11 GTPases, plus Rabin-8, a GDP:GTP exchange factor (GEF) for Rab8, and GTPase tethering complexes (TRAPPII), for introduction of ciliary vesicles (CVs) into the elongating cilium¹⁴. The distal appendage protein CEP19 is recruited to the mother centriole by the FGFR1 oncogene partner (FROP1)/CEP350 complex, to capture GTP-bound RABL2B, which in turn mediates ciliary entrance of IFT-B sub complexes, in early steps of protrusion^(180,181 and others). Some of the noted proteins are implicated in cancer pathogenesis (Table S1).

In **disassembly**^{11,13}, activation of Aurora A kinase (AURKA), polo-like kinase 1 (PLK1), and NimA related kinase (NEK) family kinases are proximal signals at the basal body triggering resorption, and dependent on upstream cues provided by activators including neural precursor cell expressed developmentally down-regulated protein 9 (NEDD9), pitchfork (PIFO), histone deacetylase 6 (HDAC6) and other proteins. Transient

accumulation of Ca(2+) at the ciliary basal body stimulates calmodulin (CaM) binding and activation of AURKA, supporting ciliary disassembly¹⁶⁹. PLK1 phosphorylation of nephrocystin 1 (NPHP1) in the transition zone¹²⁰ and association with Dishevelled segment polarity protein 2 (DVL2) to activate NEDD/AURKA at the basal body¹²¹ promote ciliary disassembly¹²¹. In parallel, NEK2 interactions with the kinesin family member 24 (KIF24) at the basal body, and phosphorylated dynein light chain tctex-type 1 (DYLT1) at the ciliary transition zone, also promote the disassembly process and S phase entry (reviewed in ¹¹).

Figure 3. Ciliary signaling systems within tumors.

Signaling systems anchored at cilia. Schematic representation of cilia-based signaling components of the Hedgehog (A), Notch (B), WNT (C; canonical Wnt signaling right of dotted line, non-canonical Wnt signaling left of dotted line), and PDGFRα (D) signaling systems.

A. HH ligands bind to the Patched (PTCH1) receptor, which is localized to the ciliary membrane. In the absence of HH binding, PTCH1 and G-protein-coupled receptor 161 (GPR161) provide repressive signals that sequester a second protein, Smoothened (SMO) in

intracellular vesicles outside the cilium¹⁶⁶. HH binding causes PTCH1 to be trafficked out of cilia, allowing SMO to translocate into the cilia, where it activates GLI effectors¹⁶⁷, which translocate to the nucleus and trigger transcription of GLI-targeted genes.

B. Notch pathway signaling requires cleavage of ligand-bound, activated Notch by the γ -secretase complex, localized proximal to the basal body; this releases an intracellular domain (NICD), which translocates to the nucleus as part of the CSL transcription factor complex, and induces MYC, CCND3, HES1 and other genes.

C. In the absence of Wnt ligand, the β -catenin destruction complex (DC), composed of axin, APC, PP2A, glycogen GSK3 and CK1 α , efficiently promotes β -catenin degradation by proteasome. In the canonical Wnt pathway, a Wnt ligand (e.g. WNT1–3, 8a, 8b, 10a, and 10b: blue oval) binds to Frizzled (FZ) and low-density lipoprotein receptor-related protein 5 or 6 (LRP5/6) which recruit Dishevelled (DVL) and the DC. This association inactivates the DC, allowing β -catenin to translocate to the nucleus to induce transcription of target genes (indicated by red arrows). The ciliary protein inversin/NPHP2 (INV) regulates proteasomal degradation of DVL, and hence influences accumulation of β -catenin²⁸. In the non-canonical pathway, distinct WNT ligands (e.g. WNT4, 5a, 5b, 6, 7a, 7b, and 11; blue circle) bind FZ, but INV here acts to promote DVL recruitment and activation of JNK and RHOA, regulating planar cell polarity (PCP)²⁸ (indicated by blue arrows).

D. PDGF-AA ligand binds to cilia-localized PDGFR α receptors. Downstream activation of the MEK1/2 and AKT effectors is mediated proximal to the basal body, and results in transcription of pro-proliferative genes including STATs, c-Fos, and c-Jun.

Figure 4. Paracellular signaling defects involving cilia. A.

Populations of cells in the TME have distinct patterns of ciliation for pancreatic ductal adenocarcinoma (left, PDAC), medulloblastoma (right) and influencing their ability to respond to extracellular signals with ciliary receptors. In PDACs, as cancer cells become undifferentiated, ciliation is lost, but retained on stromal cells. In medulloblastomas, cancer cells retain cilia. **B.** Examples of potential signaling disruptions associated with drug treatment of a pancreatic tumor mass with targeted therapies that have ciliary action. A SHH/SMO inhibitor will block receipt of cancer cell-derived signaling to cancer associated fibroblasts (CAFs). A PI3K or potentially an AURKA inhibitor can cause reciliation of tumor cells, and greater ciliation of stromal cell populations, increasing paracellular SHH signaling, but also creating an autocrine SHH signaling loop in tumors. In this case, the PI3K inhibitor, but not the AURKA inhibitor, will also limit the downstream consequences of the stromal to tumor signaling loop by targeting PI3K, downstream of the Insulin Like Growth Factor 1 (IGF1) and Growth Arrest Specific 6 (GAS6)/AXL receptor tyrosin kinase, in cancer cells. An Heat Shock Protein 90 (HSP90) inhibitor such as ganetespib may have complicated action, supporting general deciliation that eliminates both paracellular and autocrine cilia-mediated signaling, as well as directly inhibiting multiple signaling pathways within cancer. Consequences for other cell types within the cell mass, and for extracellular matrix, are also likely based on known signaling relationships. ECs, endothelial cells; ICs, immune cells; CKs, chemokines and cytokines; ECM, extracellular matrix.

Table 1.

Anti-cancer drugs with documented effects on ciliation.

Category	Anti-cancer drug	Targets	Effects on ciliation	References
Clinical compound	Paclitaxel	Microtubules/tubulin	Cilium elongation and structural abnormalities; induces randomly directed rotation for motile cilia	117,165–167
	Vinblastine	Microtubules/ tubulin	Blocks ciliary formation, decreases number of cilia	114,115,168
	alisertib	AURKA	Blocks ciliary disassembly	81,169
	Demecolcine (colcemid)	Microtubules/ tubulin	Blocks ciliary formation	116,165
	Docetaxel	Microtubules/ tubulin	Decreases number of cilia	168
	Cisplatin	DNA	Reduction of cilia, cilia destruction, cilium disassembly	170,171
	Carboplatin	DNA	Cilium exfoliation or deformation	172
	ganetespib	HSP90	Induces ciliary loss	126
	Imexon	Mitochondrial oxidation / loss of membrane potential	Restores ciliogenesis	124
	Itraconazole	Systemic antifungal	Prevents accumulation of SMO in the primary cilium	173
	Valproic acid (VPA)	HDAC1–5	Restores ciliogenesis Restores ciliogenesis,	85
	Gefitinib	EGFR	prevents smoke-mediated ciliary loss in airways	124,174
	Sirolimus (rapamycin)	mTOR	Restores ciliogenesis	124,175
Pre-clinical compound	Sonidegib	SMO	Cilium disassembly	140
	PHA-680632	AURKA	Restores ciliogenesis	80
	MS-275 / FK228 (romidepsin)	HDAC1, 3 / HDAC1–2	Restores ciliogenesis	85
	Geldanamycin	HSP90	Cilium lengthening	176
	LY294002	PI3K	Restores ciliogenesis	60 87
	U0126	MEK1/2	Restores ciliogenesis	60