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REVIEW

Primary cilia in cancer: structures, functions, mechanisms, and therapeutic implications

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ABSTRACT Primary cilia, microtubule-based organelles protruding from the surfaces of most eukaryotic cells, have critical roles in maintaining cellular homeostasis, by sensing, transducing, and transmitting diverse extracellular and intracellular signals through multiple signaling pathways, including the Hedgehog, Notch, and Wnt pathways. Consequently, structural or functional abnormalities in primary cilia often lead to various human diseases, including cancer. Although primary cilia are frequently absent in most cancer types, they paradoxically facilitate tumor initiation and progression in certain malignancies. Therefore, elucidating the complex interplay between primary cilia and cancer might provide novel insights for cancer treatment. In this review, we summarize current insights into the structure and function of primary cilia, explore their roles in key tumor-associated signaling pathways, and discuss emerging evidence linking ciliary dysfunction to cancer development and progression. We also highlight recent advances in targeting cilia-associated mechanisms as potential therapeutic strategies in oncology.

KEYWORDS Primary cilia; ciliogenesis; signaling pathways; cancer; targeted therapy

Introduction

Primary cilia are solitary, non-motile, microtubule-based organelles that protrude from the apical surfaces of most vertebrate cells. Despite once being considered vestigial, primary cilia are now recognized as highly specialized signaling hubs. They compartmentalize and coordinate the activities of various signaling receptors and effectors, and have central roles in several conserved signaling pathways, including the Hedgehog (Hh), Wnt, Notch, G protein–coupled receptor (GPCR), and transforming growth factor-β (TGF-β) pathways. Through these pathways, primary cilia regulate diverse biological processes, such as cell cycle progression, planar cell polarity, stem cell fate decisions, embryonic development, and organogenesis.

Accumulating evidence suggests that primary cilia are critically involved in cancer initiation, progression, and therapeutic response. In some cancers, loss of primary cilia serves as a mechanism for evading cilia-dependent tumor-suppressive signals, such as the repressive regulation of Hh signaling. In contrast, certain tumors, such as basal cell carcinoma and medulloblastoma, require functional cilia to sustain oncogenic signaling. Furthermore, the presence or absence of cilia is closely associated with cell cycle dynamics, because ciliary formation is largely restricted to quiescent or G0/G1-phase cells. Therefore, ciliation status might potentially indicate proliferative activity. From a therapeutic perspective, the structural and functional integrity of primary cilia influences the efficacy of targeted cancer therapies. Disruption of ciliogenesis can affect drug sensitivity and resistance, whereas restoration of ciliary function can enhance treatment outcomes. Small-molecule inhibitors targeting proteins involved in ciliary disassembly, such as histone deacetylase 6 (HDAC6) and Aurora A kinase, have demonstrated potential in restoring ciliation and suppressing tumor progression.

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In summary, primary cilia are essential organelles for maintaining cellular homeostasis and proper development, and their roles in cancer biology are increasingly being appreciated. Primary cilia, which act as both environmental sensors and regulators of intracellular signaling, are promising targets for cancer diagnosis and therapy, thus offering new directions for oncological research and drug development.

Structure and dynamic regulation of primary cilia

Despite their small size, typically 1–10 μm in length[1], cilia exhibit a complex, highly organized architecture that is essential for their sensory and motile functions. Cilia are generally classified into 2 types, primary cilia and motile cilia, according to their structure and function. Structurally, a typical cilium consists of 3 distinct regions: the basal body (BB), axoneme, and ciliary membrane (**Figure 1A**). The BB is derived from the mother centriole through specific modifications and gives rise to 9 doublet microtubules that extend and form the axoneme. The axoneme serves as a microtubule-based scaffold that defines the overall morphology and function of the cilium. The axoneme exhibits 2 main structural configurations: primary cilia display a "9+0" arrangement of 9 peripheral microtubule doublets without a central pair, whereas motile cilia exhibit a "9+2" configuration with an additional central microtubule pair[2,3]. During ciliogenesis, axonemal microtubules undergo acetylation, thereby enabling visualization of the primary cilia by immunofluorescence staining with antibodies to acetylated α-tubulin[4]. The axoneme is surrounded by the ciliary membrane, a specialized membrane structure that is continuous with, but compositionally distinct from, the plasma membrane[5]. This specialized membrane is enriched in a variety of specialized signaling molecules, including olfactory receptors (in nasal epithelial cells); photoreceptors (in retinal cells); and key receptors involved in the Hh, platelet-derived growth factor (PDGF), and Wnt signaling pathways. Consequently, primary cilia function as a critical sensory and signaling hub modulating several key hallmarks of cancer (**Figure 2**).

Because cilia cannot perform autonomous protein synthesis, intraflagellar transport (IFT) proteins are indispensable in ciliary biogenesis, maintenance, and function. The movement of protein particles between the axoneme and the ciliary membrane, first observed in *Chlamydomonas reinhardtii*, led to identification of the IFT system[6]. This system mediates bidirectional transport of cargo, such as ciliary precursors and signaling proteins, between the cell body and the ciliary tip, thus sustaining ciliary dynamics and signal transduction. The IFT machinery comprises 2 major complexes. First, the IFT-B complex, including 16 core proteins, is responsible for anterograde transport from the BB to the ciliary tip—a process that is driven by the motor protein Kinesin-2 and is critical for ciliary assembly and elongation. Second, the IFT-A complex (consisting of proteins such as IFT144, IFT140, IFT139, IFT122, and IFT121) facilitates retrograde transport from the ciliary tip to the base. This retrograde movement, powered by Dynein-2 (also known as IFT dynein), is critical for recycling signaling molecules and maintaining ciliary homeostasis[7]. Defects in anterograde transport proteins, such as KIF3 or IFT-B subunits (e.g., IFT88 and IFT20), frequently result in complete loss of cilia. In contrast, mutations in retrograde transport proteins (e.g., Dynein-2 or IFT-A components) often lead to malformed cilia characterized by abnormal shortening or swelling[7,8].

Because the BB is derived from the mother centriole of the centrosome, which is also responsible for mitotic spindle assembly, ciliogenesis is tightly regulated by the cell cycle. Primary cilia typically assemble during the G0/G1 phase and are disassembled at the G1/S or G2/M transition[9,10]. Ciliary assembly involves several distinct stages (**Figure 1B**). After serum starvation, distal appendage vesicles, cytoplasmic vesicles derived from the Golgi apparatus, are transported to and accumulate near the distal appendages of the mother centriole *via* motor protein-dependent mechanisms. As these vesicles fuse, they form a cap-like structure called the ciliary vesicle, which initiates axoneme elongation beneath a double-membrane sheath. The nascent cilium then docks with the plasma membrane, and ciliogenesis is completed through membrane fusion and continuity. In contrast to the well-characterized ciliary assembly process, the mechanisms of ciliary disassembly remain less well understood. Among the identified regulators, Aurora A kinase plays a critical role in promoting the disassembly of the primary cilia. After activation, Aurora A phosphorylates HDAC6, and subsequently leads to the destabilization and deacetylation of axonemal microtubules. These events ultimately drive the breakdown of primary cilia. Even quiescent cells have been reported to lose their primary cilia, typically during specific stages of programmed differentiation or in response to extracellular mechanical stress[11].

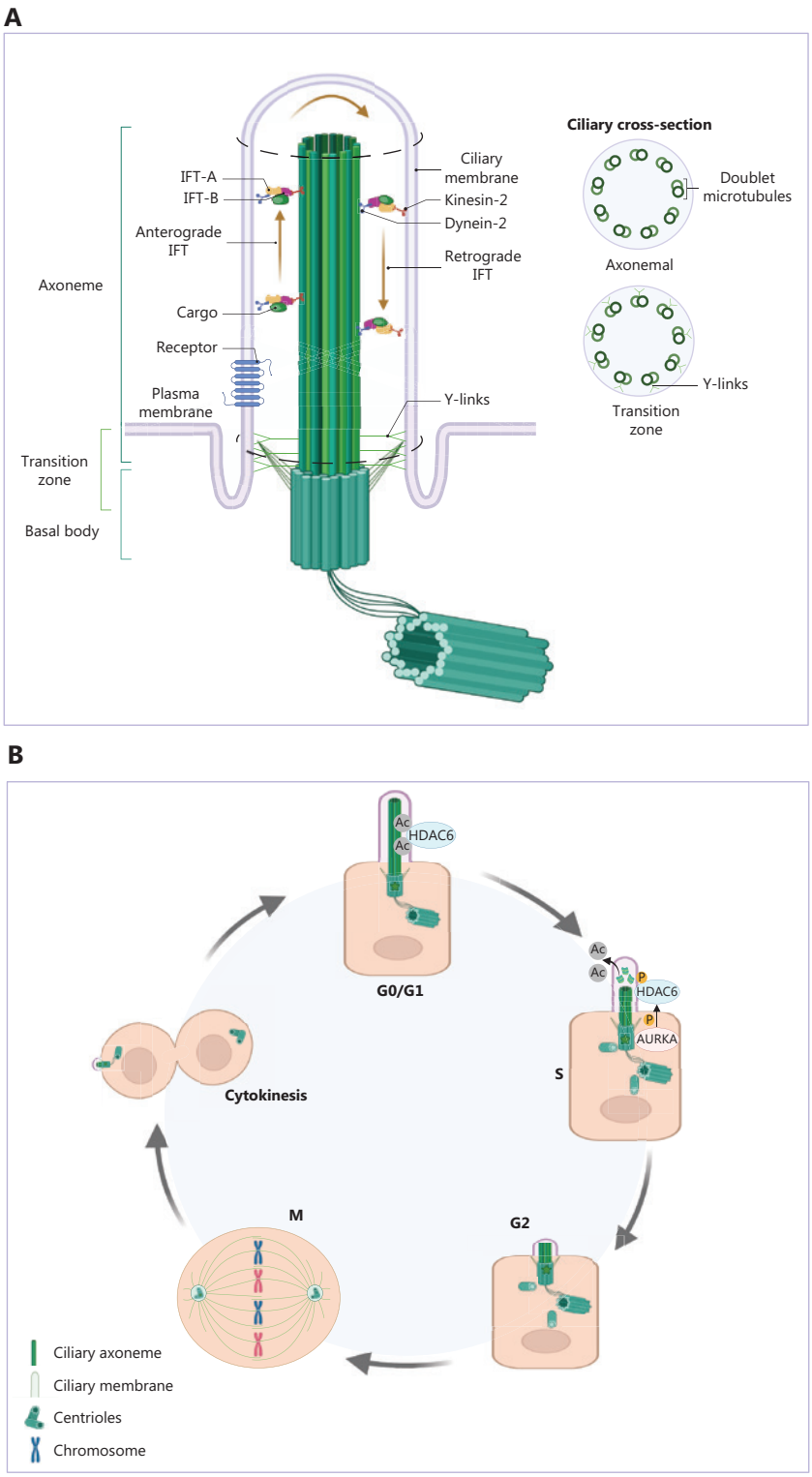

Figure 1 Structure of primary cilia and their dynamics during the cell cycle. (A) Schematic representation of primary cilia. The axoneme, composed of 9 doublet microtubules, extends from the BB through the transition zone, which contains Y-links connecting axonemal microtubules to the ciliary membrane. IFT particles mediate bidirectional trafficking, with Kinesin-2 driving anterograde transport (IFT-B complex) and Dynein-2 driving retrograde transport (IFT-A complex). The inset shows cross-sections of the cilium at the axonemal and transition zone levels. (B) Ciliary dynamics during the cell cycle. In quiescent (G0/G1) cells, a fully assembled primary cilium projects from the mother centriole. As

cells progress through the S and G2 phases, ciliary disassembly is initiated by HDAC6 and AURKA-mediated axonemal destabilization, thereby allowing centrosomes to function as spindle poles during mitosis. After cytokinesis, the centrosome-derived BB nucleates reassembly of the primary cilium in daughter cells. AURKA, Aurora kinase A; BB, basal body; HDAC6, histone deacetylase 6; IFT, intraflagellar transport.

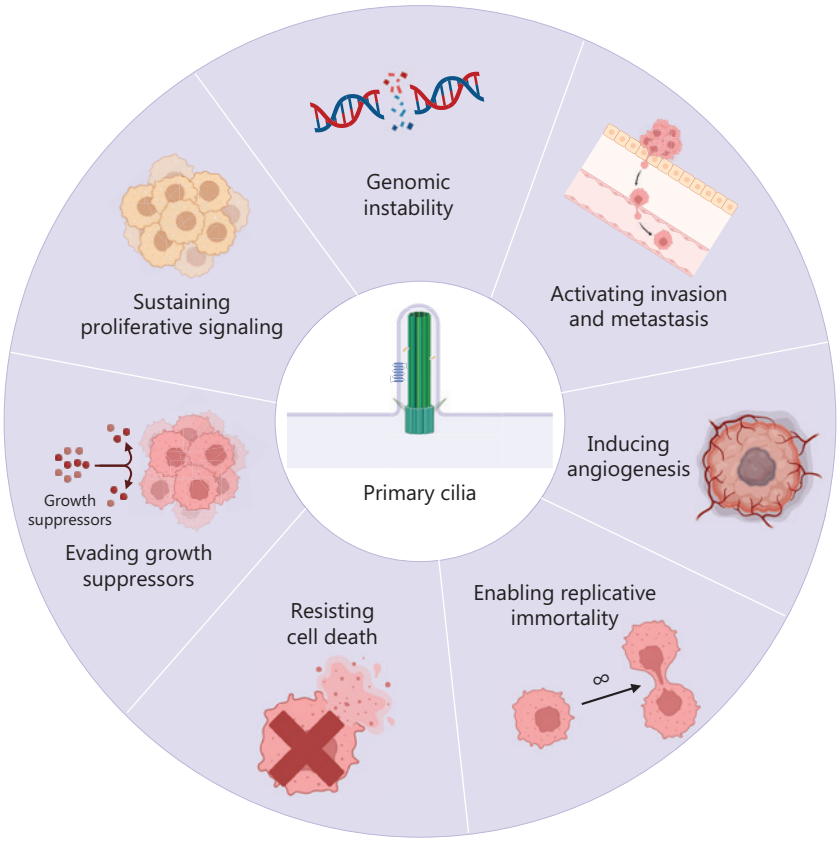

Figure 2 Primary cilia and the hallmarks of cancer. Primary cilia function as sensory and signaling organelles that orchestrate multiple critical pathways in tumor biology. Their dysfunction contributes to diverse cancer hallmarks through distinct mechanisms, as follows. **Sustaining proliferative signaling:** ciliary localization of the Hh, Wnt, and PDGF pathways promotes continuous mitogenic signaling that drives uncontrolled proliferation. **Increasing genomic instability:** defective cilia-centrosome coupling perturbs spindle orientation and chromosome segregation, thus increasing DNA damage and chromosomal instability. **Activating invasion and metastasis:** ciliary regulation of planar cell polarity and integrin signaling enhances cytoskeletal remodeling, motility, and metastatic dissemination. **Inducing angiogenesis:** cilia-mediated VEGF and HIF signaling promotes endothelial activation and neovascularization, thereby supplying tumors with oxygen and nutrients. **Enabling replicative immortality:** ciliary control of telomerase activity and stemness-associated pathways (e.g., Hh and Notch) supports self-renewal and unlimited replicative potential. **Resisting cell death:** aberrant ciliary signaling modulates the PI3K–AKT and NF-κB pathways, thereby enhancing survival under stress and protecting tumor cells against apoptosis. **Evading growth suppressors:** loss of cilia-mediated TGF-β and Hippo pathway signaling attenuates tumor-suppressive responses and enables cells to bypass anti-growth signals. Together, these processes underscore the central roles of primary cilia dysfunction in tumor initiation and progression.

Signaling pathways associated with primary cilia

Although primary cilia occupy only a tiny fraction of the total cell surface area[12], they are highly enriched in receptors involved in key signaling pathways, including somatostatin receptors; PDGF receptors; and morphogen receptors, such as those for Hh and Wnt. These cilia-localized receptors mediate the Hh and other GPCR signaling pathways, which are essential for various physiological processes such as embryonic development and cell proliferation[13].

Hh signaling pathway

The Hh gene was initially identified in *Drosophila* through genetic screening[14]. Mutant *Drosophila* embryos lacking Hh exhibit disorganized, bristle-like structures resembling the spines of a Hh, after which the gene was named. Twelve years later, the Hh protein was identified as a secreted morphogen that affects the development and differentiation of neighboring cells[15]. Subsequently, 3 homologous proteins of Hh were discovered in mammals: Sonic Hh (Shh), Indian Hh (Ihh), and Desert Hh (Dhh)[15,16]. These proteins share high sequence similarity, and can bind and activate the same signaling pathway receptors, although their expression patterns and biological functions differ[17]. Among them, Shh plays the most prominent role in embryonic development, particularly in the formation of the limb bud and neural tube[18]. Ihh regulates bone and cartilage development, and some of its functions can be compensated for by Shh. Dhh, a key regulatory factor in gonadal development, is involved in the development and formation of ovarian granulosa cells and sperm[19]. Therefore, the Shh molecule and its downstream signaling pathway are critical for proper embryogenesis.

The Shh signaling pathway is composed of several key components including the Shh ligand; its receptor, patched (Ptch1), a 12-pass transmembrane protein; smoothened (Smo), a seven-transmembrane GPCR; and downstream transcription factors known as glioma-associated (Gli) oncogenes[20]. Gli proteins contain an N-terminal transcriptional repressor domain, a central zinc finger DNA-binding domain, and a C-terminal transcriptional activation domain. In mammals, the Gli family comprises 3 members: Gli1, Gli2, and Gli3. Gli2 and Gli3 contain both activation and repression domains that endow them with dual functions. In their full-length forms, they act as activated transcription factors (GliA). After phosphorylation and proteasomal processing, cleavage of the C-terminal activation domain converts them into transcriptional repressors (GliR)[21]. Typically, Gli2 functions as an activator, whereas Gli3 is more prone to proteolytic cleavage and acts predominantly as a repressor; consequently, the Shh pathway regulates target gene expression in both positive and negative directions[22]. In contrast, Gli1 lacks the N-terminal repressor domain and functions exclusively as a transcriptional activator. Because Gli1 is a transcriptional target of GliA, and it participates in a positive feedback loop that amplifies its own expression, it is a key signal amplifier within the Hh pathway[22]. The activity of Gli proteins is tightly regulated through protein–protein interactions. Suppressor of fused (SUFU) acts as a negative regulator by binding Gli proteins, preventing their nuclear translocation, and ultimately inhibiting pathway activation[23,24] (**Figure 3A**).

In mammals, the Hh signaling pathway is functionally dependent on the presence of primary cilia[13]. Initial genetic studies revealed that mice bearing mutations in IFT-B components, such as IFT72 and IFT88, exhibit disrupted Shh signaling and phenotypes similar to those observed in Shh-null mutants[25,26]. Likewise, deletion of the kinesin motor protein KIF3 in mice leads to neurodevelopmental defects similar to those of Shh deficiency. These findings support the essential roles of intact cilia in Shh signaling. Subsequent investigations demonstrated that the IFT system is crucial for trafficking Shh pathway components within cilia[25,27]. All major elements of the pathway, including Ptch1 and Smo, are localized in the ciliary compartment and exhibit dynamic, ligand-dependent distribution along the ciliary membrane, thus highlighting the central role of primary cilia in Shh signal transduction.

In the absence of the Shh ligand, the Hh pathway remains inactive. Ptch1 and GPR161 (a ciliary GPCR) localize to the cilia, where Ptch1 prevents Smo activation and ciliary entry. GPR161 activates protein kinase A (PKA) through a cAMP-dependent mechanism, thus promoting the phosphorylation of the SUFU/Gli complex in the cytoplasm[28,29]. This phosphorylated complex is transported to the ciliary tip, where Gli proteins are further phosphorylated by casein kinase 1 (CK1) and glycogen synthase kinase 3β (GSK3β). This modification triggers proteasome-mediated cleavage of the C-terminal activation domain of Gli and generation of the repressor form (GliR), which in turn translocates to the nucleus and suppresses the transcription of downstream target genes[30,31].

After Shh ligand binding, Ptch1 undergoes lysosomal degradation *via* E3 ubiquitin ligase-mediated ubiquitination, thereby alleviating its inhibitory effect on Smo. Smo is subsequently transported to the primary cilia *via* KIF3-mediated trafficking[32,33]. Phosphorylation of its C-terminal domain by CK1 and GPCR kinase 2 (GRK2) leads to suppression of PKA activity[34,35]. Concurrently, GPR161 is removed from the cilium, and PKA signaling is further attenuated[36]. The decreased PKA activity consequently attenuates phosphorylation of the SUFU/Gli complex, which is then transported to the ciliary tip by KIF7[37]. There, phosphorylation of Gli proteins by CK1 promotes the formation of the full-length activated form, GliA.

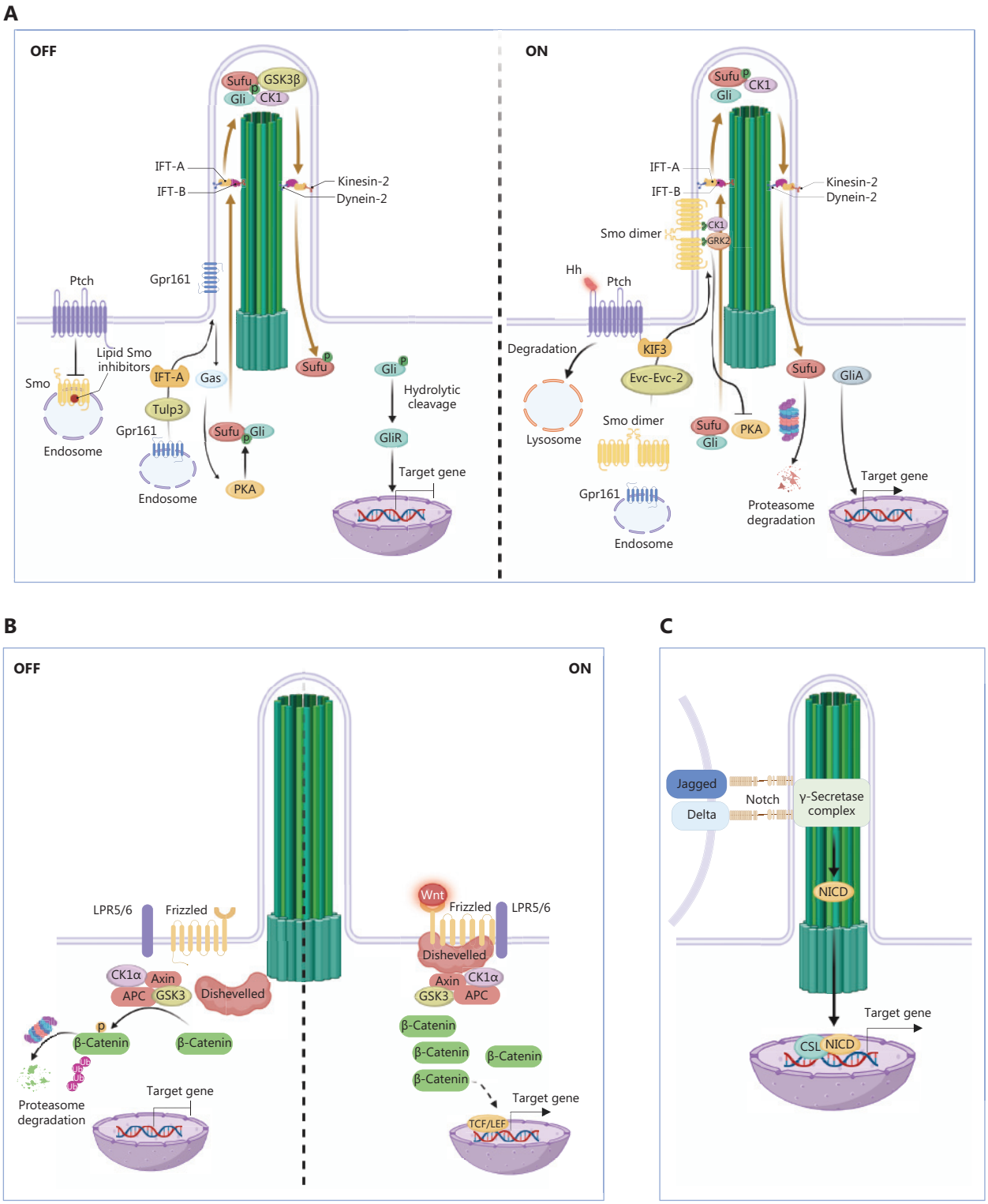

Figure 3 Primary cilia play essential roles in various signaling pathways. (A) Hh signaling in primary cilia. In the absence of Hh ligand (**OFF**), Ptch inhibits Smo, which remains inactive in the cytoplasm. Gpr161 is trafficked into cilia *via* the IFT-A complex and its adaptor Tulp3, where it activates Gαs and leads to PKA stimulation. Subsequently, the Sufu/Gli complex undergoes PKA-mediated phosphorylation and is transported to the ciliary tip. At the tip, further phosphorylation induces complex dissociation, thus allowing Gli transcription factors to be cleaved into

repressor forms (GliR) that inhibit target gene expression. In the presence of Hh ligand (**ON**), after Shh ligand binding, Ptch degradation *via* the lysosomal pathway relieves its inhibition of Smo. Smo accumulates in the cilia, and its phosphorylation by CK1 and GRK2 leads to suppression of PKA and degradation of Sufu. Consequently, Gli is activated (GliA) and translocated into the nucleus, where it drives transcription of Hh target genes. (B) Wnt signaling in primary cilia. When Wnt ligands are absent (**OFF**), β-catenin is phosphorylated by the destruction complex (Axin, APC, CK1α, and GSK3β) and targeted for proteasomal degradation, thus preventing target gene expression. When Wnt ligands are present (**ON**), the Frizzled and LRP5/6 receptors recruit Dishevelled, which in turn inhibits the destruction complex, thereby enabling β-catenin stabilization, nuclear translocation, and activation of Wnt-responsive genes. (C) Notch signaling in primary cilia. Binding of Notch ligands (Jagged/Delta) triggers γ-secretase-mediated cleavage of the Notch receptor, thus releasing the NICD. The NICD translocates to the nucleus, where it associates with CSL transcription factors and drives the expression of Notch target genes. APC, adenomatous polyposis coli; CK1, casein kinase 1; GSK3β, glycogen synthase kinase 3β; Hh, hedgehog; IFT, intraflagellar transport; LRP5/6, lipoprotein receptor-related proteins 5 and 6; NICD, notch intracellular domain; PKA, protein kinase A; Ptch, patch; Smo, smoothened; Sufu, suppressor of fused homolog; TCF/LEF, T-cell factor/lymphoid enhancer-binding factor;

Ubiquitination and degradation of SUFU *via* the proteasome pathway relieve its inhibition of Gli. Activated GliA then translocates into the nucleus and initiates transcription of target genes[38].

Wnt signaling pathway

Originally identified in the 1980s in the context of tumorigenesis, the Wnt/β-catenin signaling pathway has since been recognized as a key regulator of numerous cellular processes as diverse as early embryonic development and the maintenance of tissue homeostasis[39]. During the past 4 decades, extensive research has established its essential roles in controlling cell proliferation, migration, and differentiation. Structurally, the Wnt/β-catenin signaling pathway comprises 4 key components: the extracellular environment, membrane-associated receptors, cytoplasmic signal transduction machinery, and nuclear effectors[40]. In the extracellular space, Wnt proteins such as Wnt1, Wnt3a, and Wnt5a function as ligands that initiate signaling by binding membrane receptors, including low-density lipoprotein receptor-related proteins 5 and 6 (LRP5/6), and members of the Frizzled (FZD) family.

In the cytoplasm, signal transduction is mediated by a multiprotein complex comprising GSK3β, CK1, Dishevelled (Dvl), adenomatous polyposis coli (APC), and the scaffold protein AXIN. These components cooperatively regulate the stabilization and nuclear translocation of β-catenin, a central effector of the pathway. In the nucleus, β-catenin interacts with T-cell factor/lymphoid enhancer-binding factor (TCF/LEF) transcription factors, and subsequently drives the expression of downstream target genes such as matrix metalloproteinases and c-Myc. Notably, both endogenous and exogenous modulation of any of these 4 structural domains by agonists or antagonists can lead to either activation or inhibition of the Wnt/β-catenin pathway[40]. Wnt signaling is tightly regulated by the presence of Wnt ligands. After ligand binding to FZD and LRP5/6 at the cell surface, the cytoplasmic destruction complex comprising APC, CK1, GSK3β, and AXIN is recruited to the membrane and functionally inactivated. This inhibition prevents degradation of β-catenin, which subsequently accumulates in the cytoplasm, translocates to the nucleus, and associates with TCF/LEF transcription factors, thus modulating downstream gene expression[41]. In contrast, in the absence of Wnt ligands, the signaling cascade remains inactive. Under these conditions, FZD and LRP5/6 remain unbound, and the destruction complex remains active in the cytoplasm, where it promotes the phosphorylation and proteasomal degradation of β-catenin. This process effectively prevents β-catenin from entering the nucleus and initiating transcriptional activation of target genes (**Figure 3B**)[42].

Wnt signaling exhibits a complex and sometimes controversial relationship with primary cilia, because regulatory mechanisms have been reported to vary across cell types and species. Notably, accumulating evidence suggests that primary cilia inhibit the canonical Wnt/β-catenin pathway. For example, primary cilia suppress CK1-dependent phosphorylation of Dvl, thereby limiting Wnt pathway activation. Loss of KIF3a leads to constitutive phosphorylation of Dvl and hyperactivation of Wnt signaling, thus indicating a negative regulatory role of cilia in this pathway[43]. Another study has demonstrated that primary cilia suppress canonical Wnt/β-catenin signaling pathway by regulating the subcellular localization of Jouberin and decreasing its ability to promote β-catenin nuclear translocation[44]. Signal transduction within this pathway also depends on certain ciliary proteins, including Inversin and GSK3, a finding that further underscores the regulatory influence of cilia on Wnt signaling[44,45]. In contrast, non-canonical Wnt

signaling, which controls planar cell polarity and cytoskeletal dynamics, appears to be promoted by intact cilia[46,47]. Disruption of ciliary structure or function often leads to aberrant Wnt signaling, and contributes to developmental abnormalities and diseases including cancer[48,49]. Therefore, primary cilia play a dual role of either suppressing or promoting Wnt signaling, depending on the cellular context and pathway subtype.

Notch signaling pathway

The relationship between the Notch signaling pathway and primary cilia has emerged as a major research focus, although the underlying mechanisms remain incompletely understood. The Notch signaling pathway is activated when the extracellular domain of a Notch ligand binds a Notch receptor (Notch1–4)[50,51]. After ligand binding, the receptor is cleaved by the γ-secretase complex located near the BB of the primary cilia, thus resulting in release of the Notch intracellular domain (NICD)[51,52]. The NICD then translocates to the nucleus, where it acts as a transcription activator promoting target gene expression[53] (**Figure 3C**).

The role of primary cilia in the Notch signaling pathway appears to be tissue-specific. Because of current limitations in understanding of the Notch pathway, only a concise overview is provided herein. The primary cilia is believed to play a regulatory role in signal transduction during this process, by potentially contributing to the processing of the Notch receptors or modulating downstream cellular responses through ciliary proteins. Studies have suggested that the structural integrity and functional competence of the cilium are essential for proper Notch signaling. Disruption or loss of ciliary function might lead to aberrant Notch pathway activity, and consequently affect processes such as development, cell differentiation, and the onset of related diseases[54,55].

Deficiency in primary cilia in cancer cells

Primary cilia have recently been recognized as critical regulators of tumorigenesis. Nevertheless, their roles in cancer development and metastasis appear to be highly context-dependent, varying by cancer type and tissue cellular composition. Accumulating evidence indicates that defects in primary cilia are present in most cancers, with several notable exceptions (**Table 1**)[56-72]. This section focuses on the underlying mechanisms driving the progression of tumors in which ciliary regulation has been relatively well characterized.

Pancreatic cancer

Pancreatic ductal adenocarcinoma (PDAC), accounting for more than 90% of all pancreatic cancer cases, is characterized by high aggressiveness and poor prognosis. *KRAS* mutations are present in more than 90% of PDAC cases. Most PDACs are believed to arise from pancreatic intraepithelial neoplasia (PanIN), a well-recognized precursor lesion. Loss of primary cilia is an early hallmark of PDAC, and several studies have investigated the relationship between primary cilia and PDAC. In a study using the *Orpk* mouse model of polycystic kidney disease, the Hebrok group has reported a remarkable decrease in both the number and length of primary cilia in pancreatic tissue[73]. Similarly, the Seeley group has demonstrated that loss of primary cilia is an early and consistent feature of PDAC. In both human PDAC tissues and *KRAS*-driven mouse models, cilia have been found to be absent in nearly all PanIN and cancer cells, but to be retained in adjacent normal or acinar-to-ductal metaplasia ductal cells. This absence of cilia is independent of cell proliferation or centrosome abnormalities. Interestingly, because pharmacological inhibition of KRAS downstream pathways, particularly PI3K and MEK, restores ciliogenesis *in vitro*, KRAS signaling appears to actively suppress ciliary formation during pancreatic tumorigenesis[74].

Loss of cilia promotes malignant transformation in PDAC through several mechanisms. One novel pathway involves HDAC2, a cilia-regulating protein identified in PDAC, which cooperates with KRAS in suppressing the assembly of primary cilia *via* modulation of Aurora A kinase, thereby promoting PDAC cell proliferation[56]. Additionally, Hh signaling components are highly expressed in both PDAC and PanIN[57]. The ablation of primary cilia induces hyperactivation of the Hh signaling pathway, and consequently leads to pancreatic tissue dedifferentiation, developmental defects, and impaired endocrine function[58]. Furthermore, SOX9 and KRAS synergistically accelerate PDAC progression[75]. SOX9, a key transcription factor in pancreatic cancer, promotes tumor malignancy by downregulating ciliogenesis-associated genes and upregulating epithelial cell adhesion molecule, thus leading to ciliary defects and cellular dedifferentiation[59]. Interestingly, the role of cilia in PDAC appears to be context dependent. For example, glutamine deficiency promotes epithelial–mesenchymal

Table 1 Functional overview of primary cilia across cancer types

Cancer type	Ciliary status	Function	Mechanisms	References
PDAC	Lost	Tumor suppression	The HDAC2–KRAS–Aurora A axis inhibits ciliogenesis, thus enhancing Hh signaling and proliferation.	56-59
	Abundant	Tumor promotion	The MLPH–PLCG1 axis induces ciliogenesis, thus driving epithelial–mesenchymal transition and metastasis.	60
Breast cancer	Lost	Tumor suppression	Ciliary loss impairs Gli-dependent Hh signaling and activates Wnt signaling, thus accelerating cancer progression.	61-64
Renal cancer	Lost	Tumor suppression	VHL mutations destabilize microtubules, thus promoting ciliary disassembly *via* β-catenin and Aurora A.	65
Melanoma	Lost	Tumor suppression	EZH2 overexpression induces ciliary loss and Wnt activation, thus promoting growth and metastasis.	66,67
Medulloblastoma	Abundant	Tumor promotion	Cilia activate Smo–PKA–Gli2 signaling, thus driving tumor growth.	68
Glioblastoma	Lost	Tumor suppression	Ciliary loss disrupts the Shh, PDGF, and Wnt pathways, thus enhancing proliferation and aggressiveness.	69,70
Ovarian cancer	Lost	Tumor suppression	Loss of cilia suppresses Hh and PDGF signaling, thus promoting tumorigenesis.	71
Prostate cancer	Lost	Tumor suppression	Unciliated cells accumulate nuclear β-catenin, thus activating Wnt signaling and promoting neoplasia.	72

EZH2, enhancer of Zeste homolog 2; Gli, glioma-associated; HDAC2, histone deacetylase 2; Hh, hedgehog; MLPH, melanoma-like protein; PDAC, pancreatic ductal adenocarcinoma; PDGF, platelet-derived growth factor; PKA, protein kinase A; Smo, smoothened.

transition and metastasis in PDAC by upregulating melanoma-like protein (MLPH), which in turn facilitates formation of primary cilia and phosphorylates phospholipase C gamma 1 (PLCG1)—an effect associated with poor prognosis in patients[60].

Breast cancer

Breast cancer ranks first among cancers diagnosed in women globally and accounts for 23.8% of all cancer cases in women reported in 2022[76,77]. Several studies have identified that a decrease in primary cilia is a notable phenomenon in breast cancer[78]. According to immunofluorescence analysis, primary cilia are more frequently observed in normal human breast epithelial cells than in breast cancer epithelial cells. Moreover, in an isogenic series of cell lines representing increasing cellular transformation and tumorigenic potential, the abundance of primary cilia has been found to inversely correlate with both transformation status and tumorigenicity under serum-containing culture conditions. Therefore, loss of primary cilia might be associated with the progression of breast tumorigenesis[79]. The mammary gland is composed of ductal epithelial and basal cells, the latter of which exhibit greater abundance of primary cilia. In agreement with this observation, the McDermott group has analyzed the number and length of primary cilia in normal and cancerous breast tissue samples from 86 patients. In all 3 grades of ductal carcinoma in situ (DCIS, a precursor to invasive breast cancer), the abundance of primary cilia in basal cells was significantly lower than that in normal epithelial and basal cells. Whereas epithelial cells in DCIS grades 1 and 2 did not exhibit significantly less ciliation than normal tissue, grade 3 epithelial cells showed markedly diminished ciliation. These findings indicate that loss of primary cilia occurs in early stages of breast cancer development[80].

Another study has indicated that diminished numbers of primary cilia and the presence of ciliary structural abnormalities impair ductal extension and branching, and hinder mammary tree development[61]. Numerous studies have shown that Wnt signaling promotes the formation of mammary placodes and is essential for the initiation of mammary morphogenesis. Additionally, the Hh signaling pathway is involved in both normal ductal architecture and the malignant transformation of mammary ducts[62,63]. Interestingly, in cilia-deficient mice, classical Wnt signaling is enhanced, and the Hh pathway is suppressed[61]. In agreement with these findings, loss of primary cilia, in synergy with oncogenic signaling, particularly through inhibition of the Hh signaling pathway, has been shown to dramatically accelerate breast tumor progression and metastasis[64].

Given the established role of primary cilia in modulating the Hh signaling pathway, by converting Gli transcription factors into their repressor forms and suppressing pathway activation, the loss of cilia capable of mediating Smo-dependent signaling is a common feature of breast cancer cells. Therefore, inhibition of ciliogenesis might enhance aberrant Hh pathway activation and contribute to breast cancer development.

Renal cancer

Renal cell carcinoma (RCC), the most common type of kidney cancer, arises from tubular epithelial cells and encompasses several histological subtypes, including clear cell RCC (ccRCC), chromophobe RCC (chRCC), and papillary RCC. These epithelial cells possess primary cilia that extend into the tubular lumen and participate in signal transduction. Disruption of ciliary structure or function is associated with the formation of renal cysts, which might increase the risk of renal tumorigenesis. An analysis of 110 human kidney tissue samples has revealed markedly diminished frequencies of cilia in ccRCC, chRCC, oncocytoma, and sarcomatoid renal tumors[81].

The von Hippel–Lindau protein (pVHL) functions as part of an E3 ubiquitin ligase complex that targets proteins for proteasomal degradation. Under normoxic conditions, hydroxylation of hypoxia-inducible factor-1α (HIF-1α) on proline residues 402 and 564 enables its recognition by pVHL, which in turn facilitates its ubiquitination and degradation *via* the ubiquitin–proteasome pathway[82]. In ccRCC, large-scale genomic analyses have shown that *VHL* gene mutations are highly prevalent and occur in approximately 86.6% of cases[83]. Beyond its role in oxygen sensing, pVHL contributes to microtubule stabilization, thereby supporting the structural integrity of primary cilia[84]. In RCC cell lines, VHL knockdown activates β-catenin signaling and elevates Aurora A protein levels, both of which are known to promote ciliary disassembly[65]. Therefore, VHL loss appears to contribute to both ciliary disruption and aberrant oncogenic signaling.

Among cilia-associated genes implicated in kidney cancer, *NEK8*, which encodes a kinase involved in G2/M cell cycle transition and ciliary function, is of particular interest. Zhou et al. have demonstrated that pVHL regulates NEK8 expression by modulating hypoxia-inducible factors (HIFs) and have identified *NEK8* as a novel HIF target gene. The findings have demonstrated a pVHL-HIF-NEK8 axis linking VHL function to the maintenance of primary cilia in RCC[85]. Although *VHL* mutations are frequently observed in ccRCC, they are not sufficient to drive tumorigenesis, thus implying a need for additional genetic hits[86]. In support of this possibility, exome sequencing of tumors from triple-knockout mice lacking *VHL*, *TP53*, and *Rbl1* has revealed mutations in at least one gene associated with ciliogenesis in nearly all tumors[87]. Collectively, these findings support a contributory role of loss of primary cilia, alongside VHL inactivation, in the pathogenesis of renal carcinoma.

Melanoma

The incidence and mortality rates of melanoma, a highly aggressive malignancy originating from the malignant transformation of melanocytes, have rapidly risen in recent years. Histopathological examination remains the gold standard for melanoma diagnosis[88,89]. However, because the broad spectrum of histological and clinicopathological features often complicates the distinction between benign and malignant melanocytic lesions, more accurate tools are required to assess disease progression. In this context, the identification of reliable molecular biomarkers for early-stage, high-risk melanoma is critical. Emerging evidence suggests that the appearance and abundance of primary cilia might serve as a potential biomarker for differentiating benign and malignant melanocytic lesions[90,91]. Comprehensive analyses have revealed marked differences in ciliary abundance according to the stage of melanocytic transformation. Specifically, primary cilia are consistently present in nearly all melanocytes within benign nevi, whereas their presence is markedly diminished in melanoma in situ, invasive melanoma, and metastatic melanoma[92]. Therefore, loss of primary cilia might serve as a novel indicator of malignant progression in melanocytic tumors.

Melanoma development is associated with diverse genetic alterations including mutations in the mitogen-activated protein kinase (MAPK) cascade pathway, such as *BRAF* and *NRAS*[93-96]. Beyond genetic aberrations, epigenetic dysregulation plays a crucial role in melanoma tumorigenesis. A key epigenetic regulator is the Polycomb Repressive Complex 2, a multi-protein transcriptional repressor complex including enhancer of Zeste homolog 2 (EZH2) as a core component[97]. EZH2 catalyzes the trimethylation of histone H3 on lysine 27, which in turn leads to chromatin condensation and transcriptional silencing of tumor suppressor genes. Overexpression of EZH2 is widely associated with enhanced tumor aggressiveness, poor prognosis, and elevated recurrence in multiple cancer types[98,99].

In a melanoma mouse model, Zingg et al. have demonstrated greater EZH2 expression in melanoma than benign nevi. Genetic depletion of EZH2 decreases tumor growth and metastasis while prolonging survival *in vivo*. The authors further established a mechanistic link among EZH2, ciliary disassembly, and melanoma progression. Their findings have demonstrated that EZH2 suppresses the expression of ciliogenesis-associated genes and results in loss of primary cilia; subsequently, activation of the oncogenic Wnt/β-catenin signaling pathway promotes melanoma metastasis. Collectively, these results reveal a pathogenic cascade wherein elevated EZH2 expression drives ciliary disassembly and Wnt/β-catenin pathway activation, and ultimately facilitates melanoma progression and metastasis[66,67].

Primary cilia and the tumor microenvironment

The interplay between primary cilia and the tumor microenvironment (TME) has emerged as a critical determinant of cancer progression. As specialized sensory organelles, primary cilia mediate the integration of diverse extracellular cues from the TME, including soluble signaling molecules (cytokines and growth factors), extracellular matrix components, and mechanical stimuli. In contrast, TME-derived factors extensively modulate the biology of primary cilia through multiple mechanisms, such as hypoxia signaling pathways, inflammatory factors, metabolic reprogramming, and biomechanical forces. This bidirectional communication underscores the importance of primary cilia in modulating tumor behavior in response to microenvironmental cues.

In response to serum-deprived conditions, tumor cells upregulate NPHP3 expression and promote formation of primary cilia through activation of the ROS-ERK-HIF-1α signaling axis. This adaptive response enables tumor cells to cope with nutrient scarcity and is a critical survival strategy in nutrient-deprived TMEs[100]. Hypoxia, a hallmark of solid tumors, also controls the formation of primary cilia. Studies in tenocytes have indicated that hypoxic conditions markedly decrease ciliary length[101,102]. In contrast, opposing effects have been observed in Madin-Darby canine kidney cells and immortalized retinal pigment epithelial cells, in which hypoxia induces ciliary elongation[103,104]. These cell-type-specific alterations in ciliary length might modulate ciliary surface area and consequently affect cilia-mediated signaling pathways. Therefore, the interplay among hypoxia, ciliogenesis, and downstream signaling pathways requires further investigation to elucidate its role in tumor biology.

Cells continually face diverse exogenous and endogenous stressors that induce DNA damage, and consequently activate the DNA damage response (DDR) system and its associated repair pathways. Beyond its well-established roles in chromosome segregation and genome stability maintenance, the centrosome functions as a key platform for formation of primary cilia that links DDR to ciliary biology. Emerging evidence indicates that mutations in DDR-associated proteins not only predispose individuals to cancer but also give rise to syndromes that share clinical features with ciliopathies, most notably congenital microcephaly. This connection is supported by 2 key findings: (1) Multiple DDR components, including the cell cycle regulator CHK1, localize to centrosomes. CHK1 orchestrates cell cycle checkpoints from this organelle and facilitates centrosome duplication through interactions with the DNA repair proteins BRCA1 and NBS1, although the underlying mechanisms remain elusive[105,106]. (2) Environmental stressors dynamically redistribute proteins between centrosomes and DNA damage sites. For example, the centriolar protein CEP164 translocates to UV-induced DNA lesions, where it participates in ATR-mediated checkpoint activation and base excision repair, thus directly linking ciliary proteins to DDR machinery[107,108].

Primary cilia function as signaling hubs that integrate multiple stress response pathways, and maintain constant crosstalk with the DDR system and cell cycle regulators. This interconnection provides critical insights into the DDR-cilia relationship. Notch signaling exemplifies this link: direct interactions have been demonstrated between Notch pathway components and the DDR machinery. Notably, Notch receptors bind and inhibit ATM kinase activity across evolutionarily diverse species, including mammals, *Xenopus laevis*, and *Cryptobacterium hidradenum*[109], thus suggesting an evolutionarily conserved mechanism for Notch-mediated DDR modulation. Recent research has revealed a bidirectional relationship between primary cilia and DDR. Genotoxic stress activates the DNA-PK-p53 signaling cascade and consequently promotes ciliogenesis[110-112]. Interestingly, because the number of primary cilia normalizes after stress removal, DNA damage signaling appears to initiate and potentially sustain ciliogenesis during stress responses. In contrast, suppression of ciliogenesis regulators, such as CEP164 and IFT88, decreases DNA-PK and p53 activation[112]. These findings establish a complex reciprocal

regulation system in which primary cilia not only respond to genomic stress but also modulate DNA repair signaling pathways[113,114].

Therapeutic targets in cilia-mediated cancers

Primary cilia participate in cancer initiation and progression, and their assembly and disassembly are tightly controlled by several key regulators, including HDAC6, Aurora A, and EZH2. Therefore, targeting these regulators provides attractive strategies for cancer treatment. Multiple inhibitors of these regulators have been developed (**Table 2**)[115-129].

HDAC6

The axonemal structure of primary cilia is composed of acetylated α-tubulin, whose acetylation promotes microtubule stability and maintenance of primary cilia. HDAC6, a cytoplasm-localized deacetylase[118,130], removes acetyl groups from α-tubulin and consequently decreases microtubule stability. Under certain signaling or stress conditions, HDAC6 activation leads to microtubule deacetylation, thus triggering ciliary disassembly or resorption. Aberrant HDAC6 activity can disrupt the structure and function of primary cilia, and impair cilia-dependent signaling pathways such as Hh and Wnt[131,132]. The association between HDAC6 overexpression and ciliary loss in several cancers suggests a potential role of this enzyme in tumorigenesis *via* ciliogenesis suppression[133,134]. Therefore, HDAC6 inhibition might provide a potential therapeutic strategy.

As described above, primary cilia are essential for tumor development in Shh-driven medulloblastoma, in which deletion of the cilia-associated genes KIF3a and IFT88 significantly suppresses tumorigenesis in mouse models. However, this dependency is subtype specific, because primary cilia promote tumor growth in Wnt-driven medulloblastoma[68]. In cholangiocarcinoma (CCA), cilia are frequently lost because of HDAC6-mediated mechanisms. HDAC6-induced deciliation promotes cholangiocyte proliferation; anchorage-independent growth; and activation of the MAPK and Hh signaling pathways. HDAC6 depletion or pharmacological inhibition with tubastatin A restores ciliogenesis in

Table 2 Inhibitors targeting regulators of primary cilia

Target	Compound	Specific	Development stage	References
HDAC6	ACY-1215	Yes	Clinical use	115
	ACY-241	Yes	Clinical use	116
	Tubastatin A	Yes	Research use only	117
	Nexturastat A	Yes	Used in preclinical studies	118
	Vorinostat	Pan-HDAC	Clinical use	119
	Panobinostat	Pan-HDAC	Clinical use	120
Aurora A	Alisertib (MLN8237)	Yes	Clinical use	121
	MLN8054	Yes	Discontinued because of dose-limiting adverse effect	122
	VX-680 (Tozasertib)	Pan-Aurora	Halted because of toxicity and limited efficacy	123
	ENMD-2076	Pan-Aurora	Clinical use	124
EZH2	Tazemetostat (EPZ-6438)	Yes	Clinical use	125
	GSK126	Yes	Research use only	126
	CPI-1205	Yes	Clinical use	127
	Valemetostat (DS-3201)	EZH1/EZH2	Clinical use	128
	UNC1999	EZH1/EZH2	Research use only	129

EZH, Zeste homolog; HDAC6, histone deacetylase 6.

CCA cells, suppresses malignant phenotypes, and markedly decreases tumor growth *in vivo*. These findings underscore the critical role of primary cilia in CCA tumorigenesis and validate HDAC6 as a therapeutic target[135]. Similarly, in glioblastoma, HDAC6 promotes tumor growth by inducing disassembly of primary cilia. HDAC6 inhibition alters primary cilia structure in tumor cells, and consequently decreases proliferation and enhances differentiation. Notably, the absence of these effects in cilia-deficient glioma cells confirms the cilia-dependent nature of HDAC6's oncogenic role[131]. Overall, the HDAC6–cilia axis regulates the assembly and function of primary cilia, and its dysregulation in tumors such as CCA and glioblastoma underscores the therapeutic potential of HDAC6 inhibitors.

Aurora A

Aurora A, also known as serine/threonine-protein kinase 6, is a key regulator of ciliary disassembly that promotes microtubule deacetylation and ciliary resorption through activation of downstream effectors such as HDAC6 and Polo-like kinase 1. Aurora A overexpression in various cancers correlates with loss of primary cilia, whereas its inhibition restores ciliogenesis and suppresses cell cycle progression[136,137]. For instance, the observation that aberrant Aurora A activation drives loss of primary cilia in oral squamous carcinoma suggests that Aurora A inhibition might serve as an effective therapeutic strategy[138]. In cystic kidney diseases, Enhancer of filamentation 1 enhances the Aurora A-HDAC6 axis and facilitates disassembly of primary cilia. Targeting this pathway to inhibit Aurora A activity restores formation of primary cilia and decreases tumor cell migration, thus further highlighting the therapeutic potential of modulating the Aurora A-HDAC6 pathway[137].

EZH2

EZH2, a member of the Polycomb group family of epigenetic regulators, mediates transcription repression and has emerged as both a potential biomarker and therapeutic target in melanoma[99,139]. Inhibition of EZH2 suppresses tumor growth, metastasis, and invasion, and therefore is promising for melanoma treatment. Interestingly, several compounds, including clofibrate, gefitinib, sirolimus, imexon, and dexamethasone, have been reported to restore ciliogenesis in various cancer cell lines, and therefore might find potential applications in therapies targeting cilia-dependent pathways[139-141].

Discussion

Primary cilia serve as crucial signaling hubs that integrate multiple oncogenic and tumor-suppressive pathways, including Hh, Wnt, PI3K/AKT, and DNA damage repair signaling. However, how these pathways are precisely coordinated, or potentially compete, within the ciliary compartment during tumor progression remains to be fully elucidated. Additional complexity is introduced by tumor heterogeneity (including dramatic variability in the presence, length, composition, and signaling activity of cilia), thus resulting in highly context-dependent roles that can either promote or suppress tumorigenesis.

Another critical consideration involves the therapeutic targeting of ciliary regulators. Although pharmacological inhibition of proteins such as HDAC6, Aurora A kinase, and EZH2 has shown promising preclinical efficacy, clinical translation faces several challenges, including (1) variable dependence on cilia across tumor subtypes; (2) potential antagonistic effects in combination treatments with conventional therapies such as SMO inhibitors or microtubule-targeting agents; and (3) the current lack of reliable biomarkers to monitor ciliary status and functionality in patients.

In the future, several key priorities must be addressed to advance the therapeutic potential of cilia-targeting strategies in precision oncology. First, combinatorial treatment regimens should be optimized, for example, through sequential approaches that initially promote ciliogenesis, followed by selective inhibition of ciliary signaling pathways. Second, the development of robust, real-time biomarkers is crucial for monitoring ciliary dynamics *in vivo* and guiding therapeutic decision-making. Third, improving patient stratification through comprehensive molecular profiling is necessary to enable the identification of subpopulations most likely to benefit from cilia-directed therapies. A systematic and integrated investigation of ciliary biology, its interplay with the TME, and its responsiveness to rational drug combinations will be essential to achieve the full clinical potential of cilia-targeting interventions.

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Conflict of interest statement

No potential conflicts of interest are disclosed.

Author contributions

Conceived and designed the review: Jun Zhou, Yijie Wang
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