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The role of the primary cilium in cancer

Minireview

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As a common lethal disease, cancer is now responsible for the majority of deaths worldwide and has been the single most important barrier to increasing life expectancy in the world. The pathogenesis of cancer has been the key point of cancer therapeutics research. The primary cilium, a solitary microtubule-based organelle, is considered to be an important sensor for receiving mechanical and chemical stimulation from other cells and environments; it plays an important role in a variety of signal transduction and disease processes. More importantly, the primary cilium can also function as an elaborate structure to regulate cell proliferation because ciliogenesis regulates cell division by sequestering the centriole. Recently, many new findings have suggested that the length and incidence of the primary cilium are closely connected to carcinogenesis and responses to cancer therapy. Here, we review relevant evidences proving that the primary cilium plays a key role in the occurrence and treatment of cancer. We also summarize the primary cilium-associated signaling pathways in cancer, including Wnt signaling, Hedgehog signaling, PDGFR signaling, and Notch signaling, and anticipate that targeting proteins localized in the primary cilium may be a potential anti-cancer strategy.

Key words: primary cilium, cancer, signaling pathways, length

The primary cilium is an isolated, non-motile organelle that composes of a microtubule core axon and originates from the mother centriole of the centrosome, which extends from many types of eukaryotic cell surfaces to an extracellular environment [1]. The cilium was observed as a vestigial organelle over a century ago. However, in recent years, abundant evidences have indicated that primary cilium plays an important role in the occurrence of cancers, which dramatically changed our previous position. Two viewpoints exist regarding the function of primary cilia: First, primary cilia is considered as a kind of chemo-sensor and mechano-sensor, and is pivotal for the key of signal transduction in the cilium or basal body through various receptors, ion channels, transporter proteins, and their downstream effector molecules that are localized in the cilium or basal body; the primary cilium can sense stimuli, including fluid flow, light, electromagnetic fields, hormones, and other factors from the extracellular environment to activate intracellular signal transduction. Second, the primary cilium can act as a mitotic regulator to control the cell cycle [2, 3]. Most cells possessing a primary cilium are cells in the G0 phase or non-cycling differentiated cells. In order to grow again on each daughter cell as the cells pause at mitotic progression, the primary cilium is reabsorbed in cells, which reenter the cell cycle and mitosis [4]. Cell proliferation and cell cycle aberrations are responsible for tumorigenesis. Based on this, recent findings have suggested that the primary cilium plays a key role in carcinogenesis. In addition, ciliary length and incidence are closely interconnected with cancer therapy. Therefore, we provide an overview of the primary cilium in cancer genesis and therapy and summarize cilia-related signal transduction in cancer cells.

The basic structure of the primary cilium

The primary cilium measures approximately 1–20 μm in length and 200 nm in diameter [5], the main component of which is acetylated and glutamylated-tubulin. As shown

in Figure 1A, the classic primary cilium contains axoneme, ciliary membrane, transition zone, basal body, and intraflagellar transport (IFT) system [6]. The ciliary axoneme is composed of microtubules arranged in a doublet 9+0 organization pattern and occupies an essential role in the primary ciliary structure (Figure 1B). Primary ciliary axons lack key elements comprising the central pair of microtubules and nearby proteins so that primary cilium lack movement [7]. The axoneme is more like a scaffold, adhered by diverse protein complexes, such as kinesins and dyneins, that promotes the two-way transportation of cargo proteins along the ciliary body [8]. The entire axoneme is enclosed by the ciliary membrane, which continues with the plasma membrane of the cell and has a characteristic composition of receptor proteins owing to the ciliary transition zone. The latter root in the distal appendages of the mother center is an area between the axoneme and the basal body, deemed to be a compartment for the cilia while also providing docking sites for the movement of molecules in and out of the cilioplasm [9, 10]. The basic structure of the transition zone consists of Y-shaped linkers, a champagne glass shape that extends from the external microtubule double tube of the transition zone to the ciliary membrane, producing a stable membrane-resistant detergent [11]. Intraflagellar transport (IFT) consists of IFT particles (IFT-A and IFT-B) and their associated cargo proteins (kinesin 2 motor proteins and cytoplasmic dynein 2). The IFT-B proteins control anterograde transport with kinesin 2 motor proteins, and IFT-A proteins control retrograde transport with cytoplasmic dynein 2 along the axoneme [12, 13]. The IFT system is crucial for the formation and maintenance of primary cilium.

Carcinogenesis is accompanied by changes in the length of the primary cilium

The change in the length of the primary cilium is the main sign of morphological changes. The abnormalities of cilia morphology have functional consequences that impair cellular homeostasis, such as abnormal shape, shortened or elongated length, and increase or decrease of their number

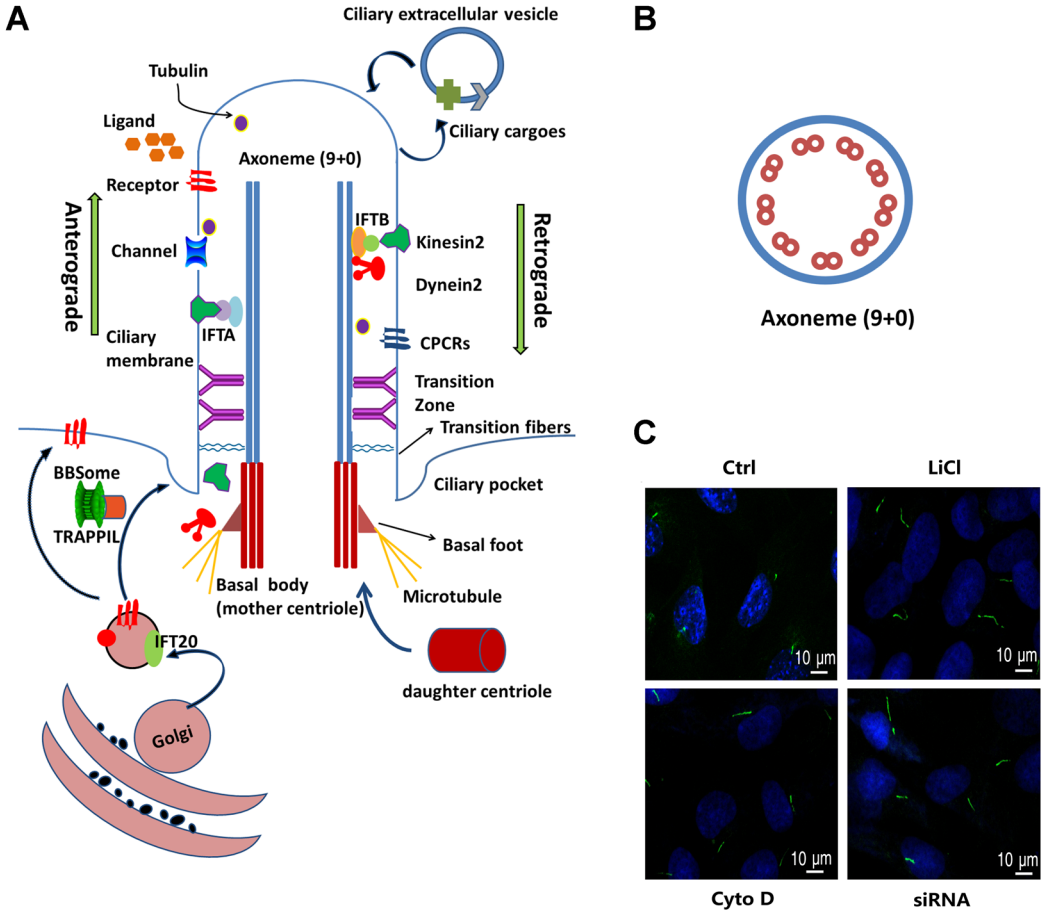

Figure 1. The structure of the primary cilium. A) The base of the cilium consists of transition fibers localized in the transition zone. Y-linkers connect the axoneme to the ciliary membrane. B) The axoneme is composed of microtubules arranged in a doublet 9+0 organization pattern. C) Immunofluorescence images of the primary cilium show that the length of the cilium can be changed after treatment [60].

[14]. The study found that function of primary cilium can be regulated by ciliary length [15]. The length of the primary cilium is 1 to 20 μm in quiescent and fully differentiated cells [16]. The length of the primary cilium is dynamically changed in the normal cell, being shortened by retraction into the cell body at the entry of cell division and elongated at differentiation [17]. The studies have proven that changes in ciliary length can be a cause or result of the development of various cancers [17]. In contrast to normal cells, primary cilium is lost in many cancers, relevant evidences show that primary cilium deficiency may be responsible for carcinogenesis [18]. Length control defects of the primary cilium are related to some clinically developmental disorders [14]. Although a number of proteins help control ciliary body length, their mechanism and the connection between ciliary length and cell cycle is still not clearly defined [15]. Further research is needed to explore the precise molecular mechanism for the length of the primary cilium in cancer.

New findings on the role of the primary cilium in cancer

As mentioned above, primary cilium is stored in the stationary or G0 phase of the cell cycle. Hence, ciliary abnormalities can disrupt the balance between cell proliferation and death, which may cause proliferative disorders such as cancer. Researchers have found the loss of cilia in multiple cancer types, and related observations suggest a suppressive role of the primary cilium in cancer development [18]. Here, we reviewed the progression of cilia in some cancers including breast cancer, ovarian cancer, and cholangiocarcinoma.

Many experiments have identified that the incidence of the primary cilium is severely reduced in breast cancer [19]. Recently, Menzl et al. demonstrated that the frequency of primary cilium was decreased in all stages and subtypes of breast cancer, and the deficiency was first observed as an early event in cancer development [20]. The loss of the primary cilium caused defects in morphogenesis and signaling, including unusual increases in Wnt signaling and decreased Hedgehog activation, promoting breast cancer progression to a more aggressive and metastatic disease [21]. Interestingly, a recent study found that the absence of the primary cilium does not necessarily represent the proliferating phases of cancer cells [19]. Kinesin Family Member 3A (KIF3A) is associated with the IFT system of the primary cilium and maintenance of ciliogenesis. The expression of motor protein KIF3A is much higher in breast cancer tissues, which is associated with the pathological change of primary cilium, and these factors may be used as diagnostic indicators and as new prognostic parameters to evaluate breast cancer [22].

For ovarian cancer, studies using bioinformatics analysis of a cancer database have found that many primary cilium-related genes are differentially expressed between ovarian cancer and normal tissues [23]. It has been proven that the ovarian cancer cell lines SK-OV3 and OVCAR3 are ciliated [24]. Studies have revealed that primary cilium can be found on the OSE and can also be detected on intralobular fibroblasts and granulosa cells in the ovary [25]. A decrease in the number of primary cilia was also found in ovarian cancer cells, and the reason is most likely the overexpression of Aurora Kinase A (AURKA), which is a major mitotic kinase that is involved in microtubule deacetylation, centrosome maturation, mitotic entry, and spindle assembly [26]. In addition, dysregulation of Hedgehog (Hh) and PDGRα signaling was also found to be responsible for the disappearance of the primary cilium; as observed in a previous experiment, the basal expression of Hh-responsive genes was increased, and the level of PDGRα protein was markedly lower, but no increase in the primary cilium was observed in OSE cells [27]. As a result, primary cilium may play an important role in the development of many cancers, although this still requires clear experimental validation.

Cholangiocarcinoma (CCA) is a rare tumor resulting from mutations in genes, especially the gene encoding localization to the primary cilium, which causes the frequency of the primary cilium to decrease sharply in CCA [28]. The loss of cilia may be related to the disorder of several molecular pathways, leading to the occurrence of CCA. For instance, Notch signaling is dysregulated upon cholangiocyte ciliary loss in CCA [29]. In addition, the absence of the primary cilium may lead to the dysregulation of mammalian target of rapamycin activity, contributing to CCA development [30]. The absence of the primary cilium due to histone deacetylase 6 (HDAC6) overexpression promotes cholangiocyte malignancy. As a tubulin deacetylase, HDAC6 is required for ciliary assembly, mediating the subsequent inhibition of tumorigenic signaling pathways such as Hedgehog and MAPK [31]. Astoundingly, SRY-related HMG-box 17 (SOX17) overexpression can induce the downregulation of HDAC6 to restore primary cilium structure and size. Therefore, HDAC6 inhibitors may be a potential treatment for cholangiocarcinoma [32]. Furthermore, a recent study demonstrated that the direct activation of LKB1 by HMC can emulate ciliary chemosensory function and inhibit tumor growth both *in vitro* and *in vivo* [33].

These observations show that the primary cilium has a tumor-suppressive function in cancer development. Restoration of the primary cilium in cancer cells can inhibit tumor cell proliferation, and it provides new ideas for cancer treatment. Hence, addressing these issues is crucial to improve our understanding of disease etiology as well as for developing new treatment approaches for cancer.

The role of the primary cilium related signaling pathways in carcinogenesis

Cilia is a very important organelle, which is involved in a series of signaling reactions. Outside-in signaling is a critical factor of the impaired signaling that induces the develop-

ment of malignant tumors. The primary cilium protrudes into the extracellular environment, and it is easily affected by extracellular signals. Primary cilia play a vital role to regulate cell signaling pathways [34]. The Hedgehog, Wnt, PDGF, and Notch signaling pathways are associated with the primary cilium.

Hedgehog (Hh) signaling transduction is crucial in the regulation of cell growth and differentiation. The Hh signaling pathway (Figure 2A) is a bona fide ciliary signaling system, and it can regulate cell self-renewal in tissue homeostasis and development. Regulation of cancer by primary cilium may be dependent on the states of the Hh signaling pathway [35]. Mouse models with IFT and ciliary defects have demonstrated that cilia are associated with Hh signaling. The studies have found abnormal activation of Hh in many cancer [36]. The primary cilium is either positive or negative regulator of Sonic Hedgehog (Shh)-related oncogenesis, depending on the initiating oncogenic mutations [37, 38]. When cilia are present, the Hedgehog component Smo and GLI inhibitors control the Hh signal; and if the cilium is lost or dysfunctional, this control may be lost, and it may lead to excessive Hh expression [39]. These findings show that primary cilia and Hh signals are associated with the carcinogenic processes and can accelerate or inhibit tumor occurrence, depending on the underlying carcinogenic factors.

The platelet-derived growth factor (PDGF) signaling pathway (Figure 2B) is another vital signal transduction pathway. PDGF and its receptors are associated with cancer and cardiovascular diseases [40]. Among the receptor tyrosine kinase pathways, PDGFR signaling is mediated by the primary cilium. Research has shown that the pathway depends on four ligands (PDGF-A, -B, -C, and -D) and two receptors (PDGFRα and PDGFRβ), and the ligands that form homodimers (PDGFRaa) and heterodimers (PDGFRab) combine with two receptors and lead to activation of the receptors [36, 41]. Furthermore, PDGFRα signaling affects multiple cellular responses and has been directly linked to the formation of human tumors, especially in gastrointestinal stromal tumors, gliomas, and osteosarcomas [42]. Therefore, the connection between primary cilium and PDGFRα signaling may open up novel avenues for the treatment of tumors.

Regulation of Wnt signaling (Figure 2C) is linked to many cancers. Some study supports the viewpoint that the cilia (or cilia-associated proteins) play an important role in restraining Wnt signaling. For example, a decrease in Hh signaling and an increase in Wnt signaling are caused by the loss of primary cilium in mammary ducts of Ift88 mutant mice [43]. Recently, the study showed that cilia or cilia-associated proteins play an important role in constraining canonical Wnt/β-catenin signaling [44]. The role of the primary cilium in Wnt signaling pathways is controversial, but cilia decomposition may play a role in tumor promotion by enhancing Wnt signaling activity and regulating cell proliferation and differentiation.

Notch signaling pathway (Figure 2D) can regulate cell survival, proliferation, fate, and communication [35]. Notch signaling transduction may depend on the primary cilium. Notch signaling induces responding of progenitor cells to SHH through increasing the length of cilia and regulating the localization of Smoothened (SMO) and Patched (PTCH1) at cilia in epidermal and neural differentiation [45–47]. Notch receptor is a TM protein with four homologous proteins (Notch1-4). Activation of the Notch signaling pathway depends on the combination of Delta-like and Jagged families Notch ligands with the receptors of the Notch1-4 [48], which regulates cell fate determination and tissue homeostasis. Activation of the Notch signaling pathway is associated with early cell lineages in development, and it makes Notch signaling to become a marker for lineage tracing [49]. Notch signaling also promotes the Shh signaling mediators into primary cilium and enhancing the responsiveness of neural progenitor cells to Shh [49].

In addition, researchers also found some other important signaling pathways to control the degradation of cilia, such as TGF-β, OFD1, and mTOR. In summary, it can be argued that the primary cilium interferes with established cancer signaling pathways through their absence or dysfunction. However, further research is urgently needed to understand the connection between primary cilium and tumor formation.

Association between the primary cilium and chemotherapy in cancer therapy

The primary cilium is also related to cancer therapeutics because the formation and length of the primary cilium in cancer tissues may change by anticancer therapy (Figure 1C). Recent studies have shown that the tip of cilia was broken and the length of cilia increased in tumor cells after treatment with antineoplastic drugs [50]. Khan et al. proved that restoring primary cilium in cancer cells was a promising new method to inhibit tumor growth, and clinical data also show that a series of commonly used chemotherapeutic drugs can restore the primary cilium in cancer cells and slow cell proliferation [50]. Among the diverse cancer therapeutic drugs, the restoration of cilia was confirmed with drugs such as imexon, gefitinib, sirolimus, clofibrate, and dexamethasone. More importantly, the primary cilium is also responsible for drug resistance in cancer therapies. Several drug-resistant tumor cell lines after drug exposure showed an increase in cilia length and/or ciliogenesis, with cilia fragmentation [51]. Jenks et al. demonstrated that cilia length has an indispensable role in acquired and newly developed resistance to various kinase inhibitors [52]. Notably, a study revealed a paradoxical consequence, finding that the absence of primary cilium protects tumor cells from susceptibility to Smo inhibitors and maintains a metastable state that depends on continuous low-level Hedgehog signaling, and accordingly, the role of cilia in promoting cell death resistance depends

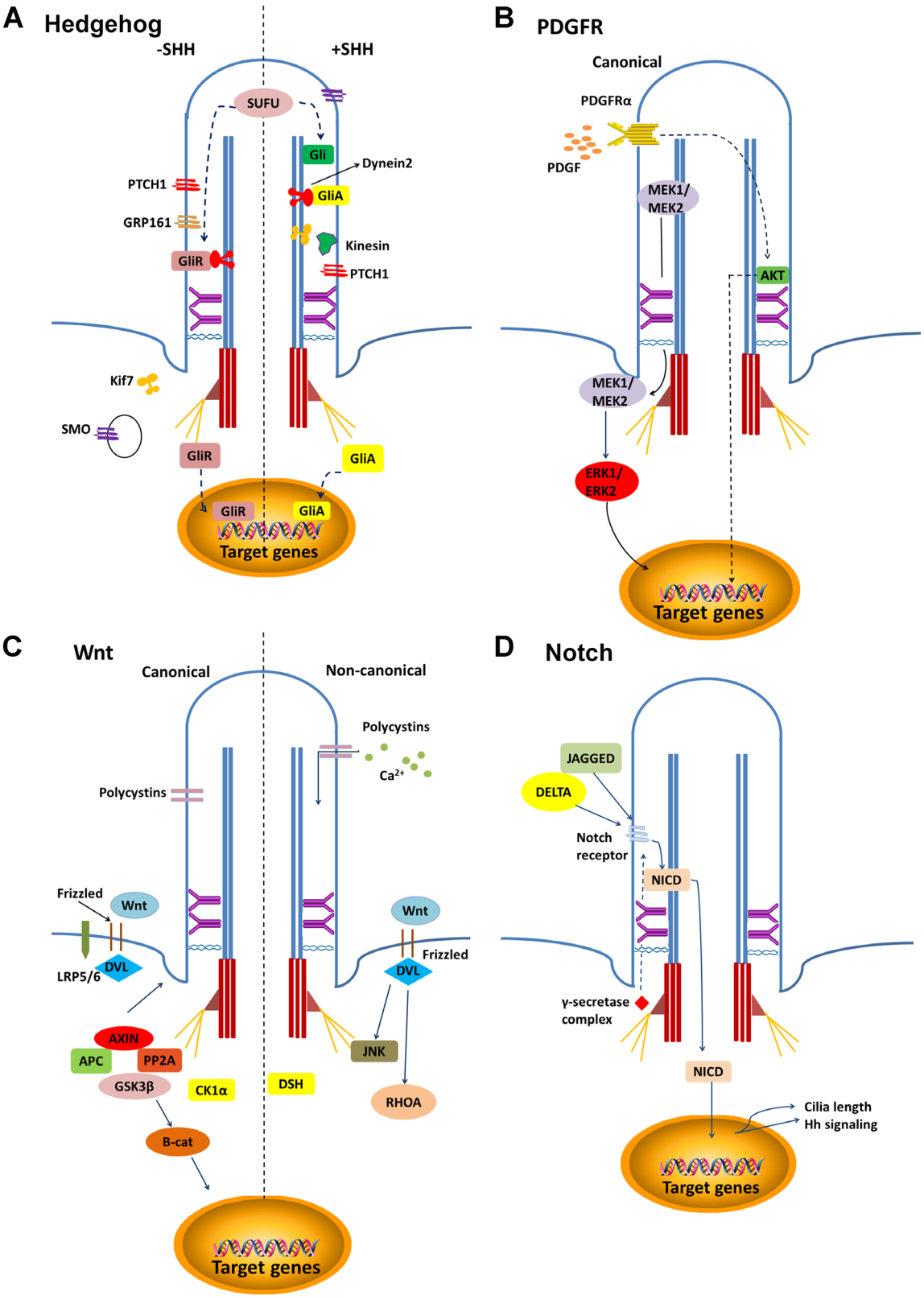

Figure 2. Various signaling cascades converge at the cilium. A) Hh signaling at the primary cilium. B) Cilium-dependent PDGFR signaling. C) Wnt signaling at the primary cilium. D) Notch signaling at the primary cilium.

on the oncogenic context [53]. However, the clear role of the primary cilium in carcinogenesis and therapy remains unclear. One reasonable hypothesis is that after using chemotherapy drugs, the proliferation of cancer cells is inhibited and the increase of the G1/G0 phase cells leads to more cells forming the primary cilium, which results in a change in the frequency of the primary cilium in cancer tissues. This conjecture may explain the change of cell frequency that has a primary cilium in cancer tissue.

Discussion

In the last few years, the primary cilium has been an active area of research, and the list of functions of cilia is growing rapidly. In particular, new dependent signaling pathways, such as ERK/MAPK signaling, TGF-b, mTOR, and OFD1 in autologous phagocytosis, were discovered in recent years, which makes it more complicated to explain the subtle mechanism of the primary cilium in signal activation. Cilia can inhibit mitosis and abnormal cell proliferation [2]. The loss of the primary cilium plays an important role in carcinogenesis. In several cancers, the primary cilium is defective or decreased in quantity. In theory, the primary cilium deficiency leads to cancer mechanisms in which ciliary dysfunction can lead to the occurrence of multiple tumors via the loss of cell cycle checkpoint control, dysregulation of cilia-mediated oncogenic signaling pathways (e.g., Hh, Wnt, and PDGFRα, etc.), alteration of proteosomal activity, and dysregulation of autophagy [18, 54, 55]. For one thing, relevant evidences show that primary cilium may play an important role in the process of tumorigenesis as an organelle of inhibiting tumor, and the loss of cilia is a common phenomenon in neoplastic transformation [56]. The restoration of primary cilium may become a potential therapeutic target. For another, primary cilium of ciliated cancer cells can provide drug resistance through the activation of the Hh pathway, turning off the Hh pathway of targeting the primary cilium may be a new therapeutic approach [41].

However, other studies reported that the loss of cilium is not associated with the cell's proliferation, suggesting that intrinsic mechanisms exist in cancer cells to avoid ciliogenesis [57–59]. Therefore, nothing is yet known about whether the primary cilium in the carcinogenesis is a primary defect or a sequential event. The understanding of the roles of the primary cilium in the human body is still in its infancy, and most biological functions of the primary cilium are unknown. Obviously, there are many exciting potential roles of the primary cilium in cell signaling and cancer that have not yet been found. Further study on the mechanism and function of primary cilium may provide new targets for cancer treatment.

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