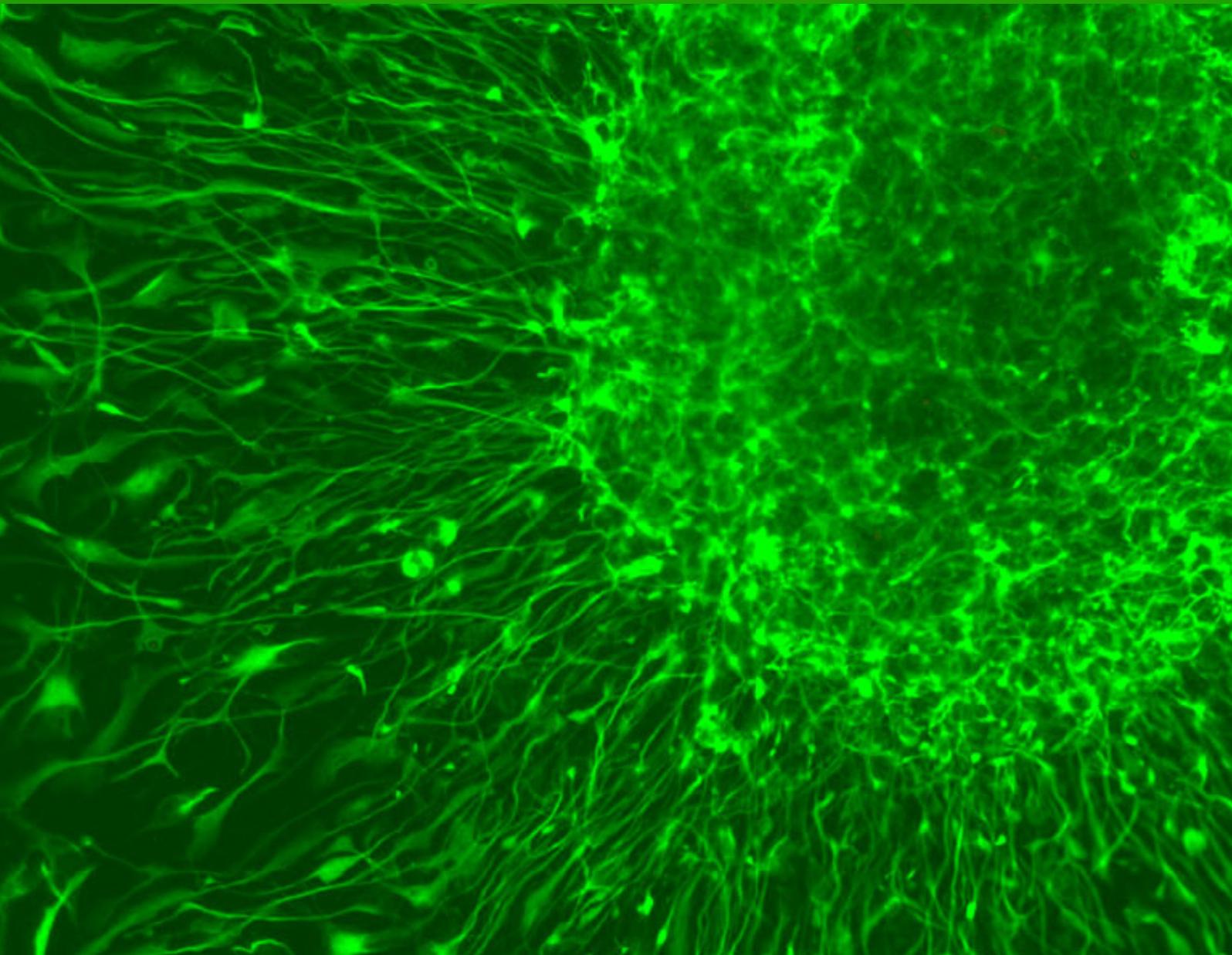


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THE ROLE OF PRIMARY CILIA IN CANCER

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ABSTRACT

Primary cilia are microtubule based organelles that sense and transduce multiple extracellular signals to the interior of the cell through several signaling pathways. Ciliary defects lead to different pathologies. Interestingly, decreased ciliary expression has been associated with different types of cancer. In this review, we discuss the function and dynamics of primary cilia, their relation to different diseases and in particular their role in cancer, and how they can be explored as potential therapeutic targets.

Keywords: primary cilia, cholangiocarcinoma, cancer, HDAC6.

Cilia functions

Primary cilia are immotile microtubule cellular based organelles present on almost every organ of the body, particularly on epithelial and stromal cells, and absent on differentiated cells of myeloid or lymphoid origin, hepatocytes, mature adipocytes and skeletal muscle [1-4]. This organelle was first observed in 1898 by the Swiss anatomist KW Zimmerman, who described the primary cilia protruding into the lumen of kidney tubules [5]. Primary cilia lengths can vary between 5-10 μm and extend outside the cell, ideally positioned to interact with the extracellular environment. Thus, the primary cilium functions like an antenna that senses the environment for different mechanic, chemo, osmotic and light signals which are transduced into intracellular pathways, generating a cellular response [1,2,6]. In this sense, cilia signaling is involved in a broad spectrum of responses such as calcium flux, cell growth, differentiation, memory and learning [7]. Among ciliated cells are the cholangiocytes, the epithelial cells that surround the hepatic lumen of intrahepatic bile ducts [8]. In particular, a cholangiocyte's cilium functions as a sensor of diverse bile stimuli, expressing proteins such as polycystin-1, polycystin-2 that serves as a mechanosensory complex on the cilia surface, TRPV4 that is a channel sensitive to minute changes in osmolarity of extracellular milieu, and P2Y12 and TGR5, which are involved in the chemosensation of biliary nucleotides and bile acids, respectively [8,9]. The decrease in length or loss of cilia has been described in several malignancies, including cholangiocarcinoma, a malignancy derived from cholangiocytes [10].

Ciliary defects also lead to diseases called ciliopathies [11]. Pathologies related with ciliary dysfunction include polycystic kidney and liver diseases (PKD), nephronophthisis, retinitis pigmentosa, Bardet-Biedl syndrome, Joubert syndrome, and the Meckel syndrome. Cholangiocytes are targets of diverse liver diseases, and abnormalities in their ciliary structure are reportedly responsible for cholangiociliopathies. For example, mutations in the genes encoding polycystin-1 or polycystin-2 can lead to Autosomal Dominant Polycystic Disease [8]. Parallelisms between some of the abnormalities found in cells involved in ciliopathies and tumoral cells have been found: loss of response to environmental signals, increased cell proliferation, cell polarity alteration and abnormal extracellular matrix control leading to fibrosis [10].

Cilia assembly and disassembly

Before studying their role in cancer, it is important to understand the dynamics of primary cilia. Their assembly begins when the cell exits the cell cycle or differentiates. When cells are quiescent, the basal body associates with a Golgi-derived vesicle and migrates to the cell surface. The assembly of primary cilia depends on a mechanism in charge of the bidirectional movement of multiprotein complexes along the axoneme known as the Intraflagellar Transport (IFT), a multimeric complex associated with motor proteins that drive ciliary cargo through the microtubular axoneme. Some components such as IFT88 are essential for proper function of this machinery and ciliary assembly [2]. The ciliary basal body is formed by centrioles that have a key role in the generation and organization of the cilium microtubules within differentiated or quiescent cells in G1/G0 [7]. Since the centriole and the basal body are equivalent, many proteins implicated in cell division are also involved with primary cilium formation in quiescent cells. Cells undergoing cell division require centrioles for accurate chromosome segregation. Consequently, when a cell reenters the cell cycle, its primary cilia are disassembled and thereby absent through the mitosis process, and the basal body turns into centrioles involved in mitotic

spindles and centrosome organization [1,6,12,13]. During the disassembly process, mammalian cells shorten their cilia through an Aurora kinase-dependent mechanism [13,14]. When the organelle disassembles, HEF1 and calcium-calmodulin activates the Aurora A kinase that phosphorylates and activates histone deacetylase 6 (HDAC6) [2,6,7,15]. HDAC6 is the protein that deacetylates the ciliary axoneme and promotes ciliary disassembly through microtubules destabilization [16].

Cilium and Cancer

Ciliogenesis is coordinated and intimately linked with the cell cycle. The cilium and mitotic spindle assemble in a mutually exclusive manner. Therefore, it has been suggested that cilium may function in a tumor suppressive environment [7]. As a matter of fact, primary cilia are lost in several types of cancer. Additionally, this structure may be involved in oncogenic signaling [17] (Table I). The loss of primary cilia has been reported in different tumoral tissues such as pancreas, breast cancer, melanoma, prostate and colon cancer [10,13]. Ovarian cancer presents a reduced number of primary cilia, and it was showed that this phenotype was linked with the overexpression of Aurora A kinase in the basal body of the cilia [18]. In renal cell carcinoma, the loss of cilia is linked with downregulation of the von Hippel-Linday (VHL) tumor suppressor gene whose inactivation leads to the induction of Hef1 and Aurora A, which consequently leads to the activation of HDAC6 [19]. Cells derived from astrocytoma/glioblastoma have been described to have an 8-25% reduction in the number of cilia [20]. The downregulation of TTLL3, a tubulin glycine ligase, leads to a reduction in the number of cilia in colon epithelium, which is associated with an increase in cell proliferation and an amplification of tumoral development in mice [21]. In pancreatic adenocarcinoma, the scenario is different as the absence of cilia is independent of ongoing proliferation and the loss of cilia can be reversed by inhibition of KRAS pathways [22].

Table 1. Cancers in which cilia are lost and the pathways/mechanisms involved

Cancer	Mechanism
Cholangiocarcinoma	Overexpression of HDAC6
Pancreas	Activation of KRAS pathways
Breast	Unknown
Prostate	Unknown
Melanoma	Unknown
Colon	Downregulation of TTLL3
Ovarian	Overexpression of Aurora A kinase
Renal cell carcinoma	Downregulation of the von Hippel-Linday
Astrocytoma/glioblastoma	Upregulation of CCRK

The frequency of cilia appearance is significantly reduced in malignant cholangiocytes both *in vivo* and *in vitro* in human patient's samples and human cells, respectively [16]. When normal cholangiocytes are deciliated using drugs such chloral hydrate or by a molecular downregulation approach using gene silencing techniques on molecules involved in ciliogenesis such as IFT88, the induction of proliferation, anchorage-independent growth and invasion were observed. Additionally, cholangiocyte deciliation also induced activation of the Hedgehog and MAPK

signaling pathways related to malignant phenotypes in cholangiocarcinoma. HDAC6, which promotes ciliary disassembly, is overexpressed in cholangiocarcinoma and decreases ciliary expression [16].

Signaling pathways regulated by primary cilia

Primary cilia loss is not the only feature that associates cilia with cancer. The WNT, mTOR, Hippo, TGF β , NOTCH and PDGF signaling pathways have all been shown to be regulated through ciliary-dependent mechanisms with diverse consequences on cell proliferation, size, differentiation, autophagy, apoptosis and tumorigenesis [17,23]. Specifically, the Sonic hedgehog (Shh) and platelet-derived growth factor (PDGF) pathways are dysregulated in different cancerous tissues and recent discoveries revealed that the primary cilium is essential for its ligand-induced activity [3]. In Shh pathway, the PTCH1 receptor is located in the ciliary membrane and, similarly, in the PDGF pathway, the receptor PDGFR colocalizes with cilia [17,24]. NOTCH1 and NOTCH3 have ciliary localization as well [17,25,26]. Moreover, TGF -RI and TGF -RII are located at the base of the primary cilia [17,27]. Since cilia have a role in the regulation of the canonical Hedgehog pathway, it was hypothesized that loss of primary cilia could stimulate tumor development in some kinds of cancer [10,28]. This hypothesis was supported with results on medulloblastoma and basal cell carcinoma [10,29]. Not only are diverse signaling pathways linked with cilia but also with factors needed to repair damaged DNA to avoid a malignant phenotype. The centrosome co-localizes with several DNA damage response factors including the DNA repair proteins BRCA1, BRCA2, PARP1, and NBS1. Additionally, it co-localizes with DNA damage response signaling kinases such as ATM, CHK1 and CHK2 and with the cell cycle checkpoint and transcriptional regulator p53 [23].

Restoration of ciliary structure/function as a therapeutic approach: Ciliotherapies

The previous information suggests that the cilium may function as a tumor suppressor organelle. Cancer cells may have developed mechanisms to inhibit ciliogenesis or increase ciliary disassembly for proliferation advantages. Since the loss of primary cilia induces a malignant-like phenotype in normal cholangiocytes, the restoration of the cilia in tumoral cells may function as a potential therapeutic approach [16].

The downregulation of HDAC6 in cholangiocarcinoma cell lines by short hairpin RNA or its inhibition with a pharmacological inhibitor, tubastatin A, induces partial cilia restoration and reverses malignant-like phenotypes. Specifically, the reduction of cell proliferation and anchorage independent growth linked with a decrease in MAPK and Hh signaling pathways activity have been observed. When these cell lines were transfected with a shRNA that targets one of the proteins of the IFT apparatus, the assembly of the cilia was irreversibly inhibited and the malignant phenotype could not be reverted using tubastatin-A. Additionally, the *in vivo* inhibition of HDAC6 reduces tumor growth and induces a partial restoration of ciliogenesis [16] (Figure 1).

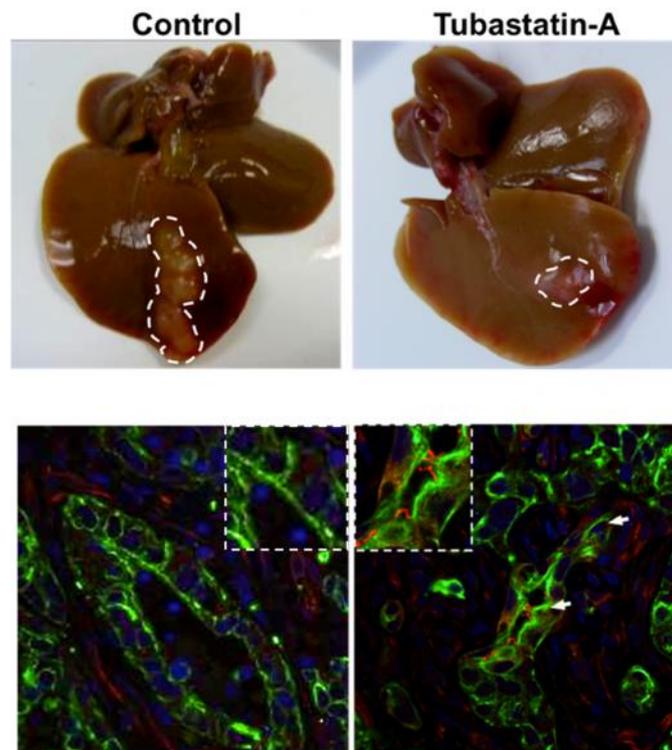


Figure 1. The *in vivo* inhibition of HDAC6 by tubastatin-A shows a reduction in liver tumor growth and partial restoration of cholangiocyte cilia [Data are from: 16]

Ciliotherapies may also be important in ciliopathies such as PKD. As a matter of fact, the use of an HDAC6 specific inhibitor, ACY1215, reduced cell proliferation and cyst growth *in vitro* and in an animal model of PKD *in vivo* [30]. The use of fenoldopam, a dopaminergic agonist that has been shown to regulate cilia length, was effective in increasing cilia length and serum nitric oxide (NO) levels, reducing blood pressure in a PDK mouse model [31]. HDAC6 was shown to have a role in PDK pathogenesis, and the pan-HDAC inhibitor trichostatin A was successful inhibiting cyst formation in PDK animal models [32]. A study on nephronophthisis (NPHP), a rare autosomal recessive disorder, showed that NPHP gene products are associated with ciliary disassembly and treatment with HDAC6 inhibitors resulted in an increase in the expression of cilia [33].

One concern with the use of HDAC6 inhibitors is the potential adverse effects, but HDAC6 knock out mice are viable and develop normally, suggesting minimal side effects [34]. Additionally, in order to increase the specificity of the pharmacological inhibitors of HDAC6, several compounds have been developed based on the structure of the enzymatic active site [35]. It is important to note that several non-selective HDAC inhibitors have been already approved by the US Food and Drug Administration (FDA) for the treatment to cancer including vorinostat, which causes an increase in ciliogenesis, romidepsin, and panobinostat [16,35].

CONCLUSION

In summary, the cilium is shown to be linked to cancer by two main mechanisms: i) its function as a sensor and transducer of different key pathways in tumoral cells such as the Hedgehog and MAPK pathways, and ii) the dynamics of the centrosome that functions as a basal body on the cilia and as a mitotic spindle organizer during cell division. Different types of cancer showed a decreased presence of cilia and when normal cells were deciliated, they acquired malignancy features. Since it has been suggested that cilia may have tumor suppressor properties different efforts have been made to inhibit its disassembly. The pharmacological inhibition of HDAC6 has been an attractive and successful approach to revert malignancies on cholangiocarcinoma cells (Figure 2). Future perspectives lead to deepen the understanding of the mechanisms involved in the inhibition of HDAC6 protection. In conclusion, designing more specific pharmacological molecules to inhibit HDAC6 would likely be a potential therapeutical approach to treat cholangiocarcinoma.

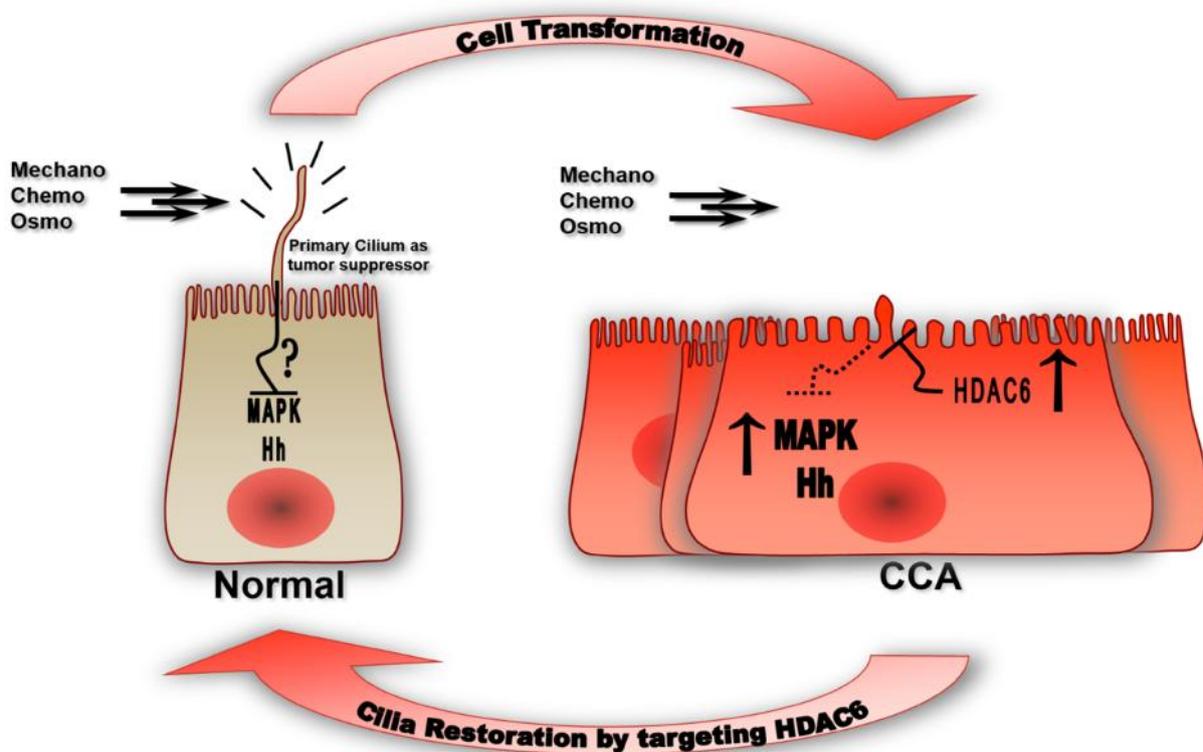


Figure 2. Working Model. Cholangiocyte primary cilia normally sense the environment and transmit those external cues into intracellular signals that function as suppressor of tumorigenic factors. Upon malignant transformation in cholangiocarcinoma (CCA), overexpression of HDAC6 induces the resorption of primary cilia, generating the disengagement between the environment and the cell interior and the derepression of tumorigenic pathways. The restoration of primary cilia through HDAC6 targeting would be a potential approach to decrease cholangiocarcinoma progression. Hh: Hedgehog.

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Estanislao Peixoto obtained his MSc (2010) in Animal Sciences from the University of Tennessee where he studied the effect of heat stress and other technical factors on IVP procedures, and obtained his PhD degree (2016) in Biomedical Sciences from the Austral University where he studied the role of SPARC on acute liver damage and liver fibrosis. He joined the laboratory of cancer cell biology and translational research on the Hormel Institute in 2017 as a postdoctoral fellow.



Adrian Pablo Mansini is a biochemist and PhD from University of Buenos Aires (U.B.A), He got his PhD in Molecular Biology. His thesis was focused on the characterization of MLL rearrangement and determination of minimal residual disease in infant acute leukemia at the Garrahan Hospital. Presently, he is a postdoctoral fellow in The Hormel Institute, University of Minnesota. He investigates the role of primary cilia in tumor biology, the mechanisms underlying the dysregulation of miRNAs in tumor cells, and the development of therapeutic approaches for Cholangiocarcinoma *in vitro* and *in vivo*.



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