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Mechanism underlying inherited renal cystic diseases

Cilia and cilia-associated proteins in cancer

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The primary cilium is a well-established target in the pathogenesis of numerous developmental and chronic disorders, and more recently is attracting interest as a structure relevant to cancer. Here we discuss mechanisms by which changes in cilia can contribute to the formation and growth of tumors. We emphasize the cancer-relevance of cilia-dependent signaling pathways and proteins, including mTOR, VHL, TSC, WNT, Aurora-A, NEDD9 and Hedgehog, and highlight the emerging role of ciliary dysfunction in renal cell carcinoma, medulloblastoma and breast cancer.

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Introduction

Almost all eukaryotic cell types can assemble a hair-like structure from their cell surface called the primary cilium (summarized in [1]). This immotile cellular organelle senses the extracellular environment to regulate intracellular signaling of multiple cell processes. The mechanistic importance of this structure in tissue development and the maintenance of tissue homeostasis is now becoming well established, yielding insights into why ciliary function is altered or lost in many different genetic diseases, including polycystic kidney disease (PKD), additional cystic kidney diseases and ciliopathies affecting other tissues (summarized in [2]). Increasingly, studies of ciliary signaling suggest that deregulation of cilia may also contribute to the pathogenesis of further common and clinically significant diseases such as cancer. This review will discuss the general mechanisms by which cilia can impact tumorigenesis, with particular focus on the signaling pathways most involved in clear cell renal cell carcinoma (ccRCC), medulloblastoma and breast cancer (BCa).

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The relevance of cilia-specified processes to cancer

Altered cell cycle dynamics, including loss of response to external signals that inhibit cell growth, increased proliferation, loss of cell polarity control and altered interaction with the cellular microenvironment, including increased or defective secretion of extracellular matrix (ECM) leading to fibrosis are among the hallmarks distinguishing a cancer cell from an untransformed normal cell [3]. Many of these defects also characterize classic ciliopathies (Fig. 1). In this context, it is particularly interesting that loss of cilia has been described in many types of solid tumor, including renal cell carcinoma [4], basal cell carcinoma [5] and breast cancer [6,7]; although, in some specific tumor types, such as medulloblastoma [8], the presence of cilia is required for cancer initiation. It is very plausible that these changes in ciliary integrity are linked to the process of tumor formation, as cell cycle regulation [9,10], planar cell polarity (PCP, also referred to as noncanonical Wnt signaling) [11–13], ECM deposition [14] and other tumor-relevant defects are now known to be specified in part by signaling proteins localized at cilia. Some studies reveal a necessity for cilia that is reminiscent of a rheostat, in which too little or too much signaling by cilia-localized protein can perturb normal cell biology [5,8], while other data indicate the oncogenic context can dictate whether loss of cilia suppresses or accelerates tumor growth [5,8]. It is currently a

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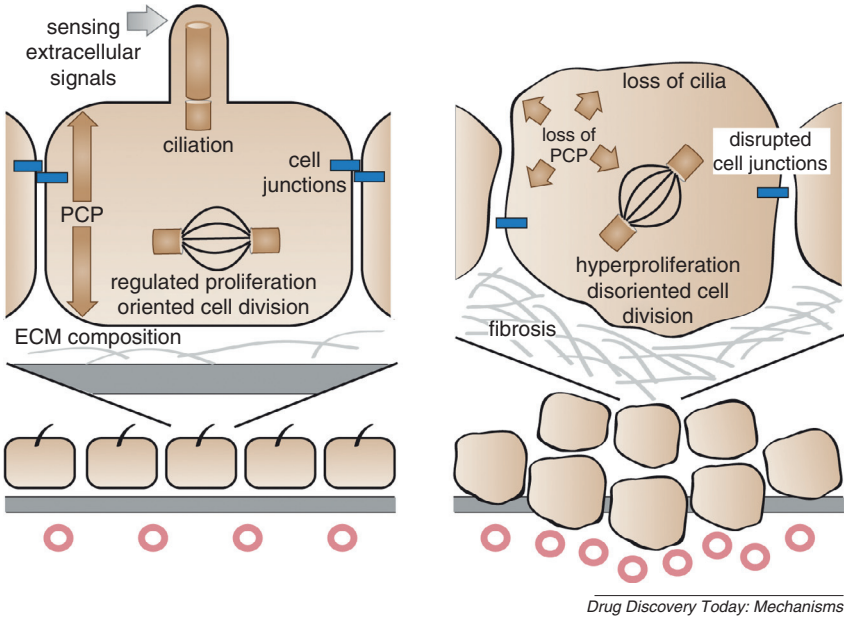

Figure 1. Cilia-associated hallmarks of transformed epithelial cells. (Left panel) The integrity of cell junctions, planar cell polarity (PCP), composition of the extracellular matrix (ECM), proliferation and oriented cell division, and sensing of some soluble extracellular signals are important features for the homeostasis of epithelial cells. (Right panel) Loss of cilia is associated with loss of PCP, hyperproliferation, disoriented cell division, disrupted cell junctions and fibrosis. Together, these defects are important hallmarks of the formation of solid tumors.

question of considerable interest as to whether changes in the cilia typically precede and contribute to cell transformation, or if oncogenic transformation subsequently induces changes in cilia that may or may not enhance the malignant potential of tumors. In this review, we will describe several cilia-linked signaling pathways in the context of tumor formation or progression.

Specific signaling pathways in carcinogenesis with ciliary links

Control of ciliary disassembly

Over the past 5 years, several proteins with confirmed roles in tumor growth have been established as regulators of ciliary resorption (Fig. 2a). In untransformed, quiescent cells, low levels of the protein AURKA (Aurora-A kinase) localizes to the basal body of the primary cilium of quiescent cells [15]. Stimuli leading to initiation of the cell division cycle induce expression and basal body localization of the AURKA activator NEDD9. Activated AURKA phosphorylates HDAC6 and other substrates, thereby triggering ciliary disassembly [15]. The AURKA-activating interaction with NEDD9 is stimulated by the binding of Ca^{2+}-liganded calmodulin to AURKA [15,16]. AURKA-NEDD9 interactions are also stabilized by an interacting PLK1-DVL2 complex at the basal body [11] and the adjacent ciliary transition zone [17]; in the normal initiation of ciliogenesis after mitosis, BUBR1 restrains DVL2 expression [18].

NEDD9, AURKA, PLK1 and BUBR1 all have previously described roles as regulators of mitotic progression, and in some cases additional functions, such as NEDD9 in integrin-dependent cell migration and invasion. Significantly, overexpression of each of these proteins also promotes tumor formation and progression. For instance, AURKA overexpression or gene amplification is associated with malignancies of breast, colon, pancreas, ovarian, bladder, liver and gastric origins; extensive interplay between AURKA and PLK1 in cancer has led each to be heavily investigated as drug targets (reviewed in [19,20]). High levels of NEDD9 enhance metastasis of numerous types of human cancer as well as multiple human cancer cell types of various origin [21]. BUBR1 dysregulation is also associated with cancer, with this predominantly attributed to dysregulation-associated defects in genomic stability and spindle checkpoints (reviewed in [22]). However, it is possible that part of the oncogenic contribution of AURKA and its interacting proteins arises from the persistent loss of cilia, cilia-associated cell cycle restrictions and growth-inhibitory signaling through cilia-localized receptors, when these are overexpressed. In support of this idea, AURKA activation at the ciliary basal body has recently been shown to rely on interactions with another partner, trichoplein [23]; interestingly, depletion of AURKA and trichoplein results in G1 cell cycle arrest unless formation of cilia is prevented by a simultaneous mutation in the IFT20 gene, suggesting that resorption of cilia may be essential for cell cycle advancement.

Cilia and cell growth controls

The mTOR pathway (Fig. 2b) integrates numerous signals related to growth factors, energy, cell stress and genotoxic