Review

Aurora A and AKT Kinase Signaling Associated with Primary Cilia

Yuhei Nishimura 1,2,*, Daishi Yamakawa 3, Takashi Shiromizu 1 and Masaki Inagaki 2,3

1 Department of Integrative Pharmacology, Graduate School of Medicine, Mie University, Tsu 514-8507, Japan; tshiromizu@med.mie-u.ac.jp
2 Global Research Center for Advanced Medical Science, Mie University, Tsu 514-8507, Japan; minagaki@doc.med.medic.mie-u.ac.jp
3 Department of Physiology, Graduate School of Medicine, Mie University, Tsu 514-8507, Japan; dyama@doc.med.medic.mie-u.ac.jp
* Correspondence: yuhei@med.mie-u.ac.jp; Tel.: +81-59-231-5006

Abstract: Dysregulation of kinase signaling is associated with various pathological conditions, including cancer, inflammation, and autoimmunity; consequently, the kinases involved have become major therapeutic targets. While kinase signaling pathways play crucial roles in multiple cellular processes, the precise manner in which their dysregulation contributes to disease is dependent on the context; for example, the cell/tissue type or subcellular localization of the kinase or substrate. Thus, context-selective targeting of dysregulated kinases may serve to increase the therapeutic specificity while reducing off-target adverse effects. Primary cilia are antenna-like structures that extend from the plasma membrane and function by detecting extracellular cues and transducing signals into the cell. Cilia formation and signaling are dynamically regulated through context-dependent mechanisms; as such, dysregulation of primary cilia contributes to disease in a variety of ways. Here, we review the involvement of primary cilia-associated signaling through aurora A and AKT kinases with respect to cancer, obesity, and other ciliopathies.

Keywords: primary cilium; aurora kinase A; AKT kinase; trichoplein; lipid raft; proliferation; differentiation; cancer; obesity; ciliopathy

1. Introduction

The human genome encodes 538 protein kinases [1] that play crucial roles in cellular homeostasis through both catalytic and noncatalytic mechanisms [2,3]. Kinase activity is subject to environmental and spatiotemporal regulation, and the consequences of protein phosphorylation are thus affected not only by the particular protein substrate but also by the cellular and subcellular context [4–6]. Therapeutic targeting of kinases most often focuses on their catalytic activity, but their noncatalytic functions are also essential to cellular homeostasis and are of increasing therapeutic interest. This is particularly true for the main focuses of this review: the serine/threonine kinases aurora kinase A (AURKA) and v-akt murine thymoma viral oncogene homolog (AKT) [4–8].

AURKA, which is itself regulated by phosphorylation and dephosphorylation, plays an essential role in mitosis through its noncatalytic function as a binding partner for several key regulatory proteins. Not surprisingly, dysregulation of this AURKA noncatalytic function is known to contribute to the development and progression of various diseases, including cancer and obesity. One example is the interaction between AURKA and microtubule nucleation factor targeting protein for xenopus kinesin-like protein 2 (TPX2) during mitosis [9]. In melanoma cells, a mutation in a key AURKA-inactivating phosphatase results in aberrant AURKA activation and its sustained interaction with TPX2 [10]. Inhibition of the AURKA–TPX2 interaction has thus been proposed as a novel therapeutic approach for melanoma with minimal effects on the proliferation of normal...
AURKA also acts as a scaffold protein and stabilizes the oncogenic transcription factor v-myc avian myelocytomatosis viral oncogene neuroblastoma-derived homolog (MYCN) by interfering with its degradation [15]. MYCN is amplified in some forms of neuroblastoma and prostate cancers and predicts poor prognosis [16,17]; therefore, inhibition of AURKA–MYCN binding might also be a useful therapeutic approach in these cancers [13,18,19].

Another clinically important kinase with crucial catalytic and noncatalytic functions is AKT. AKT lies at the crossroads of many interconnecting pathways with functions in cell metabolism, proliferation, differentiation, and survival. In addition, the conformation, but not the catalytic activity, of the AKT kinase domain plays a role in controlling the ability of the adjacent pleckstrin homology (PH) domain to bind membrane-associated lipids [20]. Thus, both catalytic and noncatalytic activities play a role in AKT function [6,21] and, similar to AURKA, AKT dysregulation plays a role in many major disorders, including cardiovascular and metabolic diseases and cancer. Taken together, these observations suggest that therapeutic approaches that specifically target kinase catalytic and noncatalytic functions in a context-dependent manner could not only improve efficacy but also minimize potential adverse effects [21–27].

Primary cilia are nonmotile, 1–10 µm long antenna-like structures that extend externally from the plasma membrane of a variety of vertebrate cells [28–34]. The cilium contains a scaffold of microtubules, the axoneme, that transports molecules into and out of the ciliary body through a process known as intraflagellar transport. The axoneme is anchored to the plasma membrane via a basal body that is derived from the mother centriole containing nine circularly arranged triplets of microtubules [29]. Primary cilia contain receptors and channels that detect signals from the extracellular milieu, such as chemical stimulation and mechanical flow, and transduce them into the cell to regulate physiological functions [28–38].

Although primary cilia are nonmotile, cilia formation is dynamically regulated in response to various stimuli [29–34,37–42]. For example, primary cilia in serum-deprived fibroblasts and retinal pigment epithelial (RPE) cells undergo disassembly upon addition of serum [43–46]. Furthermore, forced ciliation has been shown to disrupt progression of the cell cycle in proliferating human RPE cells [47–50], illustrating the importance of these organelles for proper cell function. The abundance of primary cilia is reduced in a range of cancer types, including glioblastoma [51], esophageal squamous cell carcinoma [52], colon cancer [53], cholangiocarcinoma [54,55], pancreatic ductal adenocarcinoma [56,57], clear cell renal cell carcinoma [58–61], epithelial ovarian cancer [62,63], luminally derived breast cancer [64], prostate cancer [65,66], melanoma [67,68], and chondrosarcoma [69,70], highlighting the importance of negative regulation of the cell cycle and proliferation by primary cilia [30–33,71–76].

In addition to cancer, dysregulation of primary cilia is associated with obesity [77–79]. The arcuate nucleus of the hypothalamus is composed of different types of ciliated neurons, including anorexigenic and orexigenic neurons, which express leptin receptors in the primary cilia [80]. Upon binding of leptin to the receptors, production of anorexigenic and orexigenic neuropeptides is increased and decreased, respectively, leading to appetite suppression [81,82]. Accordingly, loss of primary cilia in these neurons impairs the negative-feedback system crucial to controlling appetite [83,84]. Anorexigenic and orexigenic neuronal axons project into second-order neurons in the paraventricular nucleus that express melanocortin 4 receptor (MC4R), a common receptor for anorexigenic and orexigenic neuropeptides, and adenylate cyclase 3 (ADCY3) in the primary cilia [85]. Mutations in MC4R and ADCY3 have been associated with an increased risk of obesity and Type 2 diabetes [86–88]. Increased adipogenesis is another important cause of obesity [89]. For example, knockdown of the causative genes for Bardet–Biedl syndrome (BBS), a ciliopathy inherited in an autosomal-recessive manner, suppresses the formation of primary cilia in preadipocytes and increases adipogenesis through activation of peroxisome proliferator activated receptor γ, a master regulator of adipogenesis [90,91].
These examples serve to illustrate how breakdown in the normal physiological regulation of cilia dynamics and signal transduction can contribute to human diseases [28,33,34,92] and further highlight the role of numerous kinases in regulating primary cilia function [63,93,94]. In the remainder of this review, we focus on the association between AURKA (Section 2) and AKT (Section 3) and primary cilia function and how their dysregulation contributes to ciliopathies such as cancer and obesity (Figure 1).

Figure 1. Overview of the involvement of AURKA and AKT associated with primary cilia in cellular functions. AURKA and AKT located at the ciliary base mediate signaling from extracellular stimuli that regulate crucial cellular functions, including proliferation, differentiation, and metabolism. Among other functions, AURKA and AKT signaling regulates the assembly and disassembly of primary cilia and the dynamics of signaling hubs known as lipid rafts, which are located in the plasma membrane around primary cilia. Dysregulation of these functions contributes to a number of ciliopathies, including cancer and obesity, as described in this review.

2. Aurora Kinase a Signaling and Its Regulation in Primary Cilia

AURKA is a member of the aurora kinase family that play essential roles in regulation of the cell cycle [7,95–98]. During mitosis, AURKA is activated by autophosphorylation in a manner dependent on its interaction with distinct proteins at different stages of the mitotic process: polo-like kinase 1 (PLK1) and protein aurora borealis at G2/M [99,100], Ajuba LIM protein at prophase [101], and TPX2 at metaphase [102]. Activated AURKA stimulates mitotic entry and centrosome separation and maturation at G2/M [99,100], formation of the microtubule-organizing center, mitotic spindle organization, and chromosome alignment at M phase [103,104]. AURKA also plays important roles during G1 through promoting the disassembly of primary cilia [22,23,30–33,38,46–50,71,105,106]. Notably, formation of primary cilia is suppressed in several cancers in which expression of AURKA is increased, including epithelial ovarian cancer [63], prostate cancer [66], pancreatic ductal adenocarcinoma [57,107], and glioblastoma [108,109]. These findings suggest that inhibition of AURKA may suppress the proliferation of these cancer cells by
promoting ciliogenesis [22,30–34,38,71,74]. Various proteins have been identified as modulators of AURKA-mediated disassembly of primary cilia during G1, including trichoplein (TCHP), neural precursor cell expressed developmentally downregulated 9 (NEDD9), and centrosomal protein 55 (CEP55), which we discuss in more detail here (Figure 2).

**Figure 2.** AURKA signaling associated with primary cilia. (A) Regulation of AURKA through TCHP. In the presence of growth factors (left panel), USP8 is activated by RTK-mediated phosphorylation, leading to deubiquitination of TCHP, activation of AURKA, and suppression of ciliogenesis. In the absence of growth factor (right panel), USP8 is inactive, and TCHP is degraded via ubiquitination by CRL3-KCTD17. (B) Regulation of AURKA through NEDD9. In the presence of WNT5a (left panel), CK1ε phosphorylates DVL2, resulting in suppression of NEDD9 ubiquitination through APC10. NEDD9 activates AURKA and suppresses ciliogenesis. In the absence of WNT5a (right panel), NEDD9 is targeted for degradation by APC10-mediated ubiquitination. (C) CEP55 stabilizes AURKA. The CCT5-containing chaperonin CCT complex interacts with wild-type CEP55 and stabilizes AURKA, resulting in suppression of ciliogenesis (left panel). In cells harboring a Cys256Thr mutation in CEP55, which is associated with MARCH, mutant CEP55 fails to localize to the centrosome, leading to destabilization of AURKA and elongation of primary cilia (right panel). Abbreviations: APC10, anaphase-promoting complex subunit 10; CCT5, chaperonin-containing TCP1 subunit 5; CK1ε, casein kinase 1ε; CRL3-KCTD17, E3 ligase complex composed of cullin 3, ring-box 1, and potassium channel tetramerization domain–containing 17; Cys, cysteine; DVL2, disheveled segment polarity protein 2; MARCH, multinucleated neurons, anhydramnios, renal dysplasia, cerebellar hypoplasia, and hydranencephaly; PLK1, polo-like kinase 1; RTK, receptor tyrosine kinase; SMAD3, SMAD family member 3; Thr, threonine; Ub, ubiquitin; USP8, ubiquitin-specific protease 8; WNT5a, Wnt family member 5A.
2.1. TCHP

TCHP, originally identified as a keratin-binding protein [110,111], is a centriolar protein that suppresses the formation of primary cilia by directly interacting with AURKA [27,47–50,79]. The N-terminal 130 residues of TCHP are essential for its centriolar localization, its interaction with AURKA, and its involvement in the suppression of ciliogenesis [47]. Knockdown (KD) of TCHP in human RPE cells cultured in the presence of serum inhibits AURKA activation, induces ciliogenesis, and suppresses cell proliferation [47]; however, the effects on ciliogenesis and proliferation are suppressed by co-KD of intraflagellar transport 20 (IFT20), a protein required for primary cilia assembly [47,112]. These findings clearly demonstrate that ciliogenesis can inhibit the cell cycle and that TCHP–AURKA regulate cell proliferation via their effects on primary cilia [30–34,38,74] (Figure 2A).

TCHP expression is regulated by the ubiquitin–proteasome system [48–50]. TCHP is ubiquitinated by an E3 ligase complex composed of cullin 3, ring-box 1, and potassium channel tetramerization domain-containing 17 (CRL3\textsubscript{KCTD17}) [48]. Conversely, deubiquitination of TCHP is mediated by ubiquitin-specific peptidase 8 (USP8) [50]. KD of KCTD17 and USP8 suppresses and promotes, respectively, the formation of primary cilia in human RPE cells [48,50]. In zebrafish, knockout (KO) of kctd17 impairs ciliogenesis in Kupffer’s vesicle and induces situs inversus [74], whereas KO of usp8 increases ciliogenesis in the pronephric duct and causes renal cysts [50]. Dysregulation of AURKA is also associated with situs inversus and polycystic kidney in mice [113,114]. Thus, impairment of the TCHP–AURKA interaction may contribute to the pathophysiology of these disorders.

The activity of CRL3\textsubscript{KCTD17} in human RPE cells is unaffected by the presence or absence of serum in the culture medium [48], whereas USP8 activity is stimulated by several serum factors, including epidermal growth factor (EGF), platelet-derived growth factor, and fibroblast growth factor, each of which triggers phosphorylation of USP8 at tyrosine (Tyr) 717 and Tyr810 [50]. Activated USP8 stabilizes TCHP by suppressing its proteasomal degradation, which results in activation of AURKA, suppression of ciliogenesis, and stimulation of RPE cell proliferation [50]. KD of the EGF receptor (EGFR) in human RPE cells inhibits USP8 Tyr717 and Tyr810 phosphorylation, which enables TCHP and AURKA degradation and reverses the serum-induced effects on ciliogenesis and cell proliferation [50]. Notably, simultaneous KD of the EGFR and either IFT20 or centrosomal protein 164, both of which are indispensable for ciliogenesis, antagonizes the effects of EGFR KD on ciliogenesis and proliferation [50], supporting the hypothesis that primary cilia act as brakes on cell proliferation [30–34,38,74].

NDE1-like 1 (NDEL1), a modulator of dynein activity localized at the subdistal appendage of the mother centriole [115,116], is also involved in TCHP regulation [49]. In human RPE cells, NDEL1 is stabilized in the presence of serum and suppresses CRL3\textsubscript{KCTD17}-mediated ubiquitination of TCHP, resulting in activation of AURKA [49]. The mechanism of NDEL1 stabilization is unknown but is likely to involve inhibition of degradation, since NDEL1 undergoes proteasomal degradation in the absence of serum [49]. Interestingly, Ndel1-hypomorphic mice display increased ciliation in kidney tubular epithelial cells [49]. Given that usp8 KO in zebrafish also increases ciliation in the pronephric duct [50], these findings suggest that increased degradation of TCHP and subsequent inhibition of AURKA may be involved in the ciliation and cystic kidney defects observed in animals with NDEL1 or USP8 KD.

2.2. NEDD9

NEDD9, also known as human enhancer of filamentation 1, is another scaffold protein that affects both AURKA activation and primary cilia formation [46]. Binding of NEDD9 to AURKA, which appears to involve NEDD9 serine (Ser) 296 and the N-terminal domain of AURKA [117,118], suppresses proteasomal degradation of AURKA promoted by the ubiquitin ligase anaphase-promoting complex/C (APC/C) in MDA-MB-231 cells, a human breast cancer cell line [118].
NEDD9–AURKA signaling is regulated by several mechanisms (Figure 2B). In primary cilia in human RPE cells, binding of Frizzled receptor to its ligand Wnt family member 5A (WNT5a) stimulates a number of downstream signaling events, including activation of casein kinase 1ε (CK1ε), which phosphorylates disheveled 2 segment polarity protein 2 (DVL2) and induces formation of a complex with PLK1 and SMAD family member 3 (SMAD3) [106]. The DVL2–PLK1–SMAD3 complex inhibits APC10-induced proteasomal degradation of NEDD9, leading to activation of AURKA signaling and promotion of primary cilia disassembly [106]. Calmodulin also stimulates ciliary disassembly by increasing the interaction between NEDD9 and AURKA [105,119]. In the human esophageal squamous cell carcinoma line EC9760, peroxiredoxin 1, an antioxidant protein frequently overexpressed in tumors [120,121], increases NEDD9 expression and AURKA phosphorylation, resulting in suppression of primary cilia assembly [52]. Hyperactivation of NEDD9–AURKA signaling may thus be involved in oncogenesis through suppression of primary cilia formation [122].

Dysregulation of NEDD9–AURKA signaling is involved in several ciliopathy phenotypes. For example, cystogenesis is more extensive in mice with KO of both Nedd9 and polycystin 1 transient receptor potential channel interacting (Pkd1), a causative gene for autosomal dominant polycystic kidney disease, than in mice with KO of Pkd1 alone [123]. The mechanism of elevated cystogenesis in these mice is thought to involve a failure of AURKA activation [123]. Tetra-tricopeptide repeat domain 8 (TTC8) is involved in formation of primary cilia, and mutation of the TTC8 gene has been associated with nonsyndromic retinitis pigmentosa [124–126]. TTC8 is a member of a protein family associated with BBS [127]. A complex composed of TTC8, BBS6, and inversin stimulates ciliogenesis via suppression of NEDD9–AURKA signaling in human RPE cells [128]. Thus, mutation of BBS8 may contribute to the vision impairment associated with retinitis pigmentosa by alleviating the inhibition of NEDD9–AURKA signaling, resulting in suppression of ciliogenesis.

2.3. CEP55

Mutation of the CEP55 gene is associated with multinucleated neurons, anhydramnios, renal dysplasia, cerebellar hypoplasia, and hydranencephaly (MARCH), a lethal autosomal-recessive fetal ciliopathy [129–131]. CEP55 stabilizes AURKA by facilitating its interaction with a chaperone complex that includes chaperonin-containing TCP1 subunit 5 (CCT5) and promotes the disassembly of primary cilia in human RPE cells [132] (Figure 2C). The C-terminal of CEP55 is critical for both AURKA binding and cilia disassembly [132]. Cep55 KO mice recapitulate many aspects of MARCH, including elongation of primary cilia [132]. These findings suggest that impairment of CEP55–AURKA signaling may play a critical role in the congenital anomalies observed in MARCH.

In contrast, evidence suggest that hyperactivation of CEP55–AURKA signaling may be associated with tumorigenesis. CEP55 expression is increased in human glioma tissues and cell lines compared with normal brain tissue and cells [133,134], and high CEP55 expression in glioma is related to poor prognosis [134]. Consistent with this, suppression of CEP55 in human glioma cell lines decreases proliferation [133,134]. Of note, primary cilia are often downregulated in glioblastoma [109]. Given that AURKA has been proposed as a potential therapeutic target in glioblastoma [25], these findings suggest that inhibition of CEP55–AURKA signaling could be a novel strategy for the treatment of glioma and glioblastoma.

3. AKT Signaling and Its Regulation in Primary Cilia

The serine/threonine kinase AKT plays a crucial role in signaling pathways involved in multiple cell functions, including survival, growth, metabolism, proliferation, and differentiation [21]. AKT activation is initiated by engagement of G protein-coupled receptors or receptor tyrosine kinases that are linked intracellularly to class I phosphatidylinositol-3-kinase (PI3K) [21,135]. Activated class I PI3K phosphorylates phosphatidylinositol 4,5-bisphosphate (P(1,4,5)P2) at the plasma membrane to generate phosphatidylinositol 3,4,5-trisphosphate (P(3,4,5)P3), which then binds to the PH domain of AKT. This inter-
action recruits AKT to the plasma membrane where it is phosphorylated on threonine (Thr)308 and Ser473 by phosphatidylinositol-dependent protein 1 and mammalian target of rapamycin complex (mTORC) 2, respectively [136]. Dual phosphorylation of AKT at these sites fully activates its enzymatic activity and results in phosphorylation of various key substrates, including B-cell lymphoma-2-associated agonist of cell death, Forkhead box O3, tuberous sclerosis complex 1/2, and glycogen synthase kinase 3β (GSK3β) [135]. These AKT substrates are pivotal regulators of many cellular functions, including protein synthesis, autophagy, proliferation, and differentiation [135,136]. With respect to cilia homeostasis, AKT-mediated phosphorylation of GSK3β located at the cilia axoneme suppresses cilia assembly and stability, which contributes to various ciliopathy phenotypes [92,137,138]. The noncatalytic function of AKT is also involved in these activities [6], and AKT activation can occur in a subcellular compartment-specific manner [21,92,135,139,140]. Here, we highlight the regulation of AKT signaling in primary cilia by three mechanisms: by TCHP through altered lipid raft dynamics around primary cilia (Figure 3A), by inositol polyphosphate-5-phosphatase E (INPP5E) (Figure 3B), and by the tumor suppressor von Hippel–Lindau (VHL) protein.

**Figure 3.** AKT kinase signaling associated with primary cilia. (A) Lipid raft-mediated activation of AKT at the base of primary cilia during adipogenesis. Exposure of preadipocytes to adipogenic stimuli activates IR and IGF1R located at the ciliary base and leads to accumulation of CAV1- or GM3-positive lipid rafts, phosphorylation of AKT, and promotion of adipogenesis. KD or KO of Tchp elongates primary cilia of preadipocytes, which inhibits the accumulation of lipid rafts upon adipogenic stimulation. (B) Regulation of AKT by INPP5E. PI3K and INPP5E balance the generation of PIP3, a key activator of AKT. Loss-of-function mutation in INPP5E increase PIP3, hyperactivates AKT, and suppresses ciliogenesis, leading to cell proliferation, tumorigenesis, and anomalies. Abbreviations: CAV1, caveolin 1; GSK3β, glycogen synthase kinase 3β; INPP5E, inositol polyphosphate-5-phosphatase E; IGF1R, insulin-like growth factor 1 receptor; IR, insulin receptor; PI3K, phosphatidylinositol-3-kinase; PIP2, phosphatidylinositol 4,5-bisphosphate; PIP3, phosphatidylinositol 3,4,5-triphosphate.
3.1. TCHP

TCHP deletion has several effects on lipid metabolism associated with primary cilia in both cultured cells and mice (Figure 3A). While the primary cilia of preadipocytes are normally elongated initially and then gradually shorten during differentiation [141], TCHP KO results in longer than normal primary cilia during differentiation [79]. Various receptors located in and/or around primary cilia are involved in adipogenesis [142], including the insulin receptor (IR) [79], insulin-like growth factor 1 receptor (IGF1R) [143–145], Patched-1 and Smoothened [146], and free fatty acid receptor 4 [78]. During adipogenesis, IR/IGF1R–AKT signaling is positively modulated by lipid rafts [147,148], which are membrane nanodomains that regulate multiple cellular functions, including proliferation, differentiation, and apoptosis [149–156]. Lipid rafts act as hubs for recruitment of many signaling proteins, including components of the PI3K–AKT cascade, in response to internal and external stimuli [153,157–162]. Studies in the mouse mesenchymal progenitor cell line C3H10T1/2 have shown that exposure of the cells to adipogenic stimuli leads to accumulation of lipid rafts containing caveolin 1 (CAV1) or ganglioside GM3 around the base of primary cilia [79]. TCHP KD in these cells does not affect the localization of IRs but suppresses accumulation of CAV1- or GM3-positive lipid rafts around the ciliary base, which inhibits Akt signaling and disrupts cell differentiation to adipocytes [79]. Notably, TCHP KO mice are resistant to the deleterious metabolic consequences of a high-fat diet [79]. Taken together, these findings suggest that TCHP–AKT signaling may be a novel therapeutic target for the development of anti-obesity agents.

In addition to the accumulation of lipid rafts, TCHP KD in C3H10T1/2 cells reduces the abundance of actin filaments in primary cilia compared with control cells [163]; however, simultaneous KD of intraflagellar transport protein 88, which is required for ciliogenesis [164], ameliorates the effects of TCHP KD on cilia length, actin filamentation, CAV1- or GM3-positive lipid raft accumulation, AKT phosphorylation, and adipogenesis [79,163]. Actin filaments are thought to play important roles in the dynamics of CAV1 [165–167]. These findings suggest that TCHP may regulate AKT activity through effects on lipid raft dynamics around primary cilia [79,163].

Modulation of lipid rafts has attracted attention as a promising approach to various diseases in addition to obesity, including cancer and inflammation [162,168–170]. In addition to AKT, signaling proteins associated with other cascades, including the mitogen-activated protein kinase pathway and the Janus kinase-signal transducer and activator of transcription pathway, are assembled in lipid rafts and positively and/or negatively regulate signal transduction into the cell [129,133–138]. Prostate cancer and melanoma are both associated with a reduction in the abundance of primary cilia [65,67,72,171,172], and hyperactivation of lipid raft–AKT signaling is also observed in these cancers [21,154,156,170,173]. Stimulation of ciliogenesis via inhibition of lipid raft accumulation and suppression of lipid raft–AKT signaling around primary cilia may thus be a potential method for inhibiting the growth of melanoma and prostate cancer [163]. Nevertheless, the relationship between primary cilia and lipid rafts remains to be fully elucidated [174].

3.2. INPP5E

The activity of AKT is decreased by dephosphorylation of PI(3,4,5)P3 to PI(4,5)P2 by phosphatase and tensin homolog deleted from chromosome 10 (PTEN) and of PI(3,4,5)P3 to PI(3,4)P2 by several 5′-phosphatases, including inositol polyphosphate-5-phosphatase (INPP5) D, INPP5E, INPP5J, and INPP5K [135,175]. Among these phosphatases, INPP5E is located in primary cilia and is a regulator of AKT signaling at this location [92].

Mutations in INPP5E are associated with Joubert syndrome, a recessive neurodevelopmental ciliopathy that results in underdeveloped and malformed brain structures. The pathogenic mutations in INPP5E decrease the dephosphorylation of PI(3,4,5)P3, resulting in hyperactivation of AKT and suppression of ciliogenesis [176] (Figure 3B). In mice, conditional inactivation of INPP5E in kidney epithelial cells causes hyperactivation of AKT and mTORC1, reduced numbers of primary cilia, and polycystic kidneys [177]. Addition-
ally, deletion of INPP5E in mouse neurons causes aberrant activation of AKT signaling and impairs axon tract development [140]. KD of inpp5e in zebrafish also increases PI(3,4,5)P3 accumulation and suppresses the formation of primary cilia [178].

Mutations in INPP5E are also found in various cancers, including stomach adenocarcinoma, glioblastoma multiforme, and lung adenocarcinoma [179]. Such mutations frequently involve the phosphatase domain [179], suggesting that dysregulation of AKT signaling and primary cilia may contribute to tumor growth. In addition to the regulation of ciliogenesis, INPP5E also controls chromosomal integrity [179]. The mechanisms underlying oncogenesis associated with INPP5E mutations remain largely unknown.

3.3. VHL

VHL is an E3 ubiquitin ligase that plays an important role in the cellular response to hypoxia via its regulation of substrates such as the transcription factors hypoxia-inducible factor (HIF) 1α and 2α [180]. Under normoxic conditions, VHL binds to HIF1α that has been hydroxylated at proline (Pro) 402 and/or 564 by the enzymes prolyl-4 hydroxylase domain (PHD) 1, 2, and 3 and subsequently ubiquitinates HIF1α, leading to its degradation [181]. Under hypoxic conditions, however, the activities of PHD1–3 are inhibited, which prevents VHL-mediated ubiquitination and degradation of HIF1α [182] and increases the transcription of hypoxia-related genes.

Mutation of VHL is associated with von Hippel–Lindau syndrome, a rare inherited disorder that causes malignant and benign neoplasms and multiple cysts, especially in the kidney [183,184]. Impairment of VHL in human renal clear cell carcinoma (RCC) has been shown to inhibit the formation of primary cilia [58,137,185]. In mouse embryonic fibroblasts, VHL binds to AKT1 hydroxylated at Pro125 and Pro314 by Phd2, which results in suppression of AKT kinase activity but does not increase its degradation [186,187]. In human RPE cells, loss of primary cilia caused by VHL depletion can be rescued by AKT inhibition [188].

Biallelic inactivation of VHL is the most frequent cause of RCC [189–191]. This disease is associated with a severe reduction in the frequency of primary cilia [59] and hyperactivation of the PI3K–AKT signaling cascade [192]. Interestingly, inhibition of AKT in VHL-deficient cells decreases the expression of AURKA [188]. Therefore, inhibition of VHL–AKT signaling may be one approach to suppress the proliferation of RCC through stimulation of ciliogenesis.

4. Future Directions

The information reviewed here illustrates how elucidation of the molecular mechanisms underlying signaling by AURKA and AKT associated with primary cilia may provide valuable insights into both the physiological and pathological functions of primary cilia. In turn, these insights lay the foundation for the development of novel therapeutics for cilia-related disorders. Some approaches to drug development may include (i) small molecules that modulate the interaction between kinases and the binding partners that regulate primary cilia, (ii) small molecules that selectively promote degradation of the kinases or their binding partners, and (iii) identifying novel and druggable AURKA and AKT binding partners crucial to their functions in the context of primary cilia.

Intense work over the past few decades has resulted in the development of inhibitors that target ATP-binding sites and/or allosteric sites in multiple kinases, including AURKA and AKT [6,26,193]. More recent advances have enabled the development of agents that interfere with binding of kinases to scaffold proteins that support kinase activation [11,13,24,194–196]. During prophase and metaphase, AURKA is recruited to microtubules in mitotic spindles through the interaction between the C-terminal catalytic domain of AURKA and the N-terminus of TPX2 [197,198]. As noted earlier, this interaction is crucial for regulating the phosphorylation state and activity of AURKA, and, importantly, it is also druggable [194]. The small molecule AURKA inhibitor Aurina acts by binding to the hydrophobic pocket of AURKA where TPX2 is normally accommodated through a
conserved Tyr-Ser-Tyr motif in TPX2 [11]. Binding of AurkinA causes mislocalization of AURKA from the microtubules in mitotic spindles and inhibits its catalytic activity without affecting ATP binding [11]. Novel approaches are currently being developed to find chemical spaces in AURKA that can modulate its protein–protein interactions [199–201].

Technologies that lead to targeted protein degradation, such as proteolysis-targeting chimeras (PROTACs), protein-catalyzed capture agents (PCCs), and specific and nongenetic inhibitors of apoptosis protein-dependent protein erasers, have been successfully applied to develop novel kinase inhibitors [202–206]. For example, a PROTAC consisting of alisertib, a clinically used ATP-competitive inhibitor of AURKA [207], and thalidomide, which induces protein degradation via cereblon-containing ubiquitin ligase, results in proteolysis of AURKA and arrest of the cell cycle in MV4-11 human acute myeloid leukemia cells [5]. AKT can also be selectively degraded by a PROTAC that utilizes ipatasertib and lenalidomide as the ATP-competitive AKT inhibitor and degradation inducer, respectively [208]. Similarly, AKT degradation is induced by a PCC that employs a peptide derived from human immunodeficiency virus type 1 Tat protein as the cell-penetrating peptide and an HIF1α peptide as a VHL ligand [209]. In addition to the kinases themselves, protein degradation systems have also been designed to target kinase modulators. The protein bromodomain containing 4 (BRD4) binds to P-TEFb, a heterodimer of cyclin-dependent kinase 9 (CDK9) and cyclin T1 and promotes transcriptional elongation through phosphorylation of RNA polymerase II [210,211]. A PROTAC composed of pomalidomide linked to OTX-015, a small molecule that binds to BRD4 at the bromodomain and extra-terminal domain, induces BRD4 degradation and consequently decreases the activity of CDK9 and expression of its downstream target, MYC [212]. Thus, targeted protein degradation can be applied to develop novel inhibitors of protein–protein interactions [213].

Subcellular compartment-specific signaling can be analyzed using Förster or fluorescence resonance energy transfer (FRET) sensors fused to signal peptides. FRET sensors have been developed to analyze multiple signaling pathways, including those involving AURKA [214], AKT [139,215], cyclic adenosine monophosphate (AMP) [216,217], and calcium [218]. For example, an AURKA FRET sensor composed of AURKA within an eGFP and mCherry donor–acceptor fluorophore pair was based on the conformational change exhibited by AURKA upon autophosphorylation of Thr288 [214]. Phosphopeptide-binding domains (PBDs) have also been employed in the development of FRET biosensors to visualize kinase activity [219]. For example, Eevee-iAkt, a FRET biosensor for AKT, is composed of YPet as the acceptor fluorophore, the Forkhead-associated domain of yeast Rad53 as the PBD, an optimized peptide derived from human GSK3β as the AKT substrate sequence, and eCFP as the donor fluorophore [215]. Addition of the C-terminal region of human H-Ras and K-Ras to the C-terminal of Eevee-iAkt localizes the expression of Eevee-iAkt to raft and nonraft domains, respectively, and enables AKT activity in each domain to be analyzed [215]. Calcium and cyclic AMP signaling in primary cilia have also been successfully analyzed using FRET sensors. One example that has facilitated analysis of calcium signaling in primary cilia is composed of calmodulin as the calcium-binding domain, M13 as the calcium-bound calmodulin-binding domain, and eCFP and YPet as the donor and acceptor fluorophores, respectively. This sensor can be selectively expressed in primary cilia by linkage to the ciliary protein ADP ribosylation factor-like GTPase 13B (ARL13B) [218]. Similarly, fusion of ciliary proteins such as ARL13B with the adenyl cyclase-coupled somatostatin receptor 3 has been employed to construct FRET sensors for analysis of cyclic AMP signaling in primary cilia [217,220]. Based on these studies, it seems likely that FRET sensors could also be constructed for the analysis of AURKA and AKT signaling localized in primary cilia. A complete picture of the interactomes of subcellular compartments, including primary cilia and lipid rafts, is gradually being deciphered by studies using other novel approaches, such as proximity mapping and stable isotope labeling using amino acids in cell culture [221–223]. These approaches have been successfully used to reveal the interactome of AURKA [27] and AKT [224].
Thus, a combination of these techniques is likely to advance our understanding of the mechanisms regulating AURKA and AKT kinase signaling within and around primary cilia and may pave the way for the development of novel therapeutics for ciliopathies.

**Author Contributions:** Conceptualization, Y.N., D.Y. and M.I.; writing—original draft preparation, Y.N.; writing—review and editing, Y.N. and M.I.; visualization, T.S. and Y.N.; funding acquisition, Y.N., D.Y., T.S. and M.I. All authors have read and agreed to the published version of the manuscript.

**Funding:** This work was supported in part by funding from the Japan Society for the Promotion of Science KAKENHI (19K07318 to Y.N., 20K07356 to D.Y., 18K06890 to T.S., and 21H02696 to M.I.), the Takeda Science Foundation (to Y.N., D.Y., and M.I.), and the Naito Foundation (to M.I.).

**Institutional Review Board Statement:** Not applicable.

**Informed Consent Statement:** Not applicable.

**Data Availability Statement:** Not applicable.

**Acknowledgments:** We sincerely apologize to our colleagues whose important publications could not be cited in this review due to space limitations. We thank Anne M. O’Rourke for editing a draft of this manuscript.

**Conflicts of Interest:** The authors declare no conflict of interest.

**References**

1. Fabbro, D.; Cowan-Jacob, S.W.; Moebitz, H. Ten things you should know about protein kinases: IUPHAR Review 14. *Br. J. Pharm. 2015*, 172, 2675–2700. [CrossRef] [PubMed]

2. Cohen, P. The role of protein phosphorylation in human health and disease. The Sir Hans Krebs Medal Lecture. *Eur. J. Biochem. 2001*, 268, 5001–5010. [CrossRef]

3. Iakoucheva, L.M.; Radivojac, P.; Brown, C.J.; O’Connor, T.R.; Sikes, J.G.; Obadovcic, Z.; Dunker, A.K. The importance of intrinsic disorder for protein phosphorylation. *Nucleic Acids Res. 2004*, 32, 1037–1049. [CrossRef] [PubMed]

4. Kung, J.E.; Jura, N. Structural Basis for the Non-catalytic Functions of Protein Kinases. *Structure 2016*, 24, 7–24. [CrossRef]

5. Adhikari, B.; Bozilovic, J.; Diebold, M.; Schwarz, J.D.; Hofstetter, J.; Schröder, M.; Wanior, M.; Narain, A.; Vogt, M.; Dudvarski, Stankovic, N.; et al. PROTAC-mediated degradation reveals a non-catalytic function of AURORA-A kinase. *Nat. Chem. Biol. 2020*, 16, 1179–1188. [CrossRef] [PubMed]

6. Lazar, G.; Kostaras, E.; Vivanco, I. Inhibitors in AKTion: ATP-competitive vs allosteric. *Biochem. Soc. Trans. 2020*, 48, 933–943. [CrossRef] [PubMed]

7. Willems, E.; Dedobbeleer, M.; Digregorio, M.; Lombard, A.; Lumapat, P.N.; Register, B. The functional diversity of Aurora kinases: A comprehensive review. *Cell Div. 2018*, 13, 7. [CrossRef] [PubMed]

8. Kostaras, E.; Kaiser, T.; Lazar, G.; Heuss, S.F.; Hussain, A.; Casado, P.; Hayes, A.; Yandim, C.; Palaksas, N.; Yu, Y.; et al. A systematic molecular and pharmacologic evaluation of AKT inhibitors reveals new insight into their biological activity. *Br. J. Cancer 2020*, 123, 542–555. [CrossRef] [PubMed]

9. Ruff, E.F.; Muretta, J.M.; Thompson, A.R.; Lake, E.W.; Cyphers, S.; Albanese, S.K.; Hanson, S.M.; Behr, J.M.; Thomas, D.D.; Chodera, J.D.; et al. A dynamic mechanism for allosteric activation of Aurora kinase A by activation loop phosphorylation. *eLife 2018*, 7, e32766. [CrossRef]

10. Hammond, D.; Zeng, K.; Espert, A.; Bastos, R.N.; Baron, R.D.; Gruneberg, U.; Barr, F.A. Melanoma-associated mutations in protein phosphatase 6 cause chromosome instability and DNA damage owing to dysregulated Aurora-A. *J. Cell Sci. 2013*, 126, 3429–3440. [CrossRef]

11. Janeček, M.; Rossmann, M.; Sharma, P.; Emery, A.; Huggins, D.J.; Stockwell, S.R.; Stokes, J.E.; Tan, Y.S.; Almeida, E.G.; Hardwick, B.; et al. Allosteric modulation of AURKA kinase activity by a small-molecule inhibitor of its protein-protein interaction with TPX2. *Sci. Rep. 2016*, 6, 28528. [CrossRef]

12. Bayliss, R.; Burgess, S.G.; McIntyre, P.J. Switching Aurora-A kinase on and off at an allosteric site. *FEBS J. 2017*, 284, 2947–2954. [CrossRef] [PubMed]

13. Levinson, N.M. The multifaceted allosteric regulation of Aurora kinase A. *Biochem. J. 2018*, 475, 2025–2042. [CrossRef] [PubMed]

14. Lake, E.W.; Muretta, J.M.; Thompson, A.R.; Rasmussen, D.M.; Majumdar, A.; Faber, E.B.; Ruff, E.F.; Thomas, D.D.; Levinson, N.M. Quantitative conformational profiling of kinase inhibitors reveals origins of selectivity for Aurora kinase activation states. *Proc. Natl. Acad. Sci. USA 2018*, 115, E11894–E11903. [CrossRef] [PubMed]

15. Otto, T.; Horn, S.; Brockmann, M.; Eilers, U.; Schüttrumpf, L.; Popov, N.; Kenney, A.M.; Schulte, J.H.; Beijersbergen, R.; Christiansen, H.; et al. Stabilization of N-Myc is a critical function of Aurora A in human neuroblastoma. *Cancer Cell 2009*, 15, 67–78. [CrossRef] [PubMed]
16. Brodeur, G.M.; Seeger, R.C.; Schwab, M.; Varmus, H.E.; Bishop, J.M. Amplification of N-myc in untreated human neuroblastomas correlates with advanced disease stage. *Science* 1984, 224, 1121–1124. [CrossRef]

17. Lee, J.K.; Phillips, J.W.; Smith, B.A.; Park, J.W.; Stoyanova, T.; McCaffrey, E.F.; Baertsch, R.; Sokolov, A.; Meyerowitz, J.G.; Mathis, C.; et al. N-Myc Drives Neuroendocrine Prostate Cancer Initiated from Human Prostate Epithelial Cells. *Cancer Cell* 2016, 29, 536–547. [CrossRef] [PubMed]

18. Brockmann, M.; Poon, E.; Berry, T.; Carstensen, A.; Deubzer, H.E.; Rycak, L.; Jamin, Y.; Thway, K.; Robinson, S.P.; Roels, F.; et al. Small molecule inhibitors of aurora-a induce proteasomal degradation of N-myc in childhood neuroblastoma. *Cancer Cell* 2013, 24, 75–89. [CrossRef]

19. Gustafson, W.C.; Meyerowitz, J.G.; Nekritz, E.A.; Chen, J.; Benes, C.; Chartron, E.; Simonds, E.F.; Seeger, R.; Matthay, K.K.; Hertz, N.T.; et al. Drugging MYCN through an allosteric transition in Aurora kinase A. *Cancer Cell* 2014, 26, 414–427. [CrossRef]

20. Lučić, I.; Rathinaswamy, M.K.; Truebestein, L.; Hamelin, D.J.; Burke, J.E.; Leonard, T.A. Conformational sampling of membranes by Akt controls its activation and inactivation. *Proc. Natl. Acad. Sci. USA* 2018, 115, E3940–E3949. [CrossRef] [PubMed]

21. Sugiyama, M.G.; Fairn, G.D.; Antonesco, C.N. Akt-ing Up Just About Everywhere: Compartment-Specific Akt Activation and Function in Receptor Tyrosine Kinase Signaling. *Front. Cell Dev. Biol.* 2019, 7, 70. [CrossRef] [PubMed]

22. Korobeynikov, V.; Deneka, A.Y.; Golemis, E.A. Mechanisms for nonmitotic activation of Aurora kinases targeting in glioblastoma: From preclinical research to translational oncology. *Biochem. Soc. Trans.* 2017, 45, 37–49. [CrossRef]

23. Bertolin, G.; Tiram, M. Insights into the non-mitotic functions of Aurora kinase A: More than just cell division. *Cell. Mol. Life Sci.* CMLS 2020, 77, 1031–1047. [CrossRef]

24. Berndt, N.; Karim, R.M.; Schönbrunn, E. Advances of small molecule targeting of kinases. *Curr. Opin. Chem. Biol.* 2017, 39, 126–132. [CrossRef]

25. De Almeida Magalhães, T.; de Sousa, G.R.; Alencastro Veiga Cruzeiro, G.; Tone, L.G.; Valera, E.T.; Borges, K.S. The therapeutic potential of Aurora kinases targeting in glioblastoma: From preclinical research to translational oncology. *J. Mol. Med.* 2020, 98, 495–512. [CrossRef]

26. Martorana, F.; Motta, G.; Pavone, G.; Motta, L.; Stella, S.; Vitale, S.R.; Manzella, L.; Vigneri, P. AKT Inhibitors: New Weapons in the Fight Against Breast Cancer? *Front. Pharmacol.* 2021, 12, 662232. [CrossRef]

27. Arslanhan, M.D.; Rauniyar, N.; Yates, J.R., III; Firat-Karalar, E.N. Aurora Kinase A proximity map reveals centriolar satellites as regulators of its ciliary function. *EMBO Rep.* 2021, 22, e51902. [CrossRef] [PubMed]

28. Anvarian, Z.; Mykytyn, K.; Mukhopadhyay, S.; Pedersen, L.B.; Christensen, S.T. Cellular signalling by primary cilia in development, organ function and disease. *Nat. Rev. Neplthol.* 2019, 15, 199–219. [CrossRef]

29. Malicki, J.J.; Johnson, C.A. The Cilium: Cellular Antenna and Central Processing Unit. *Trends Cell Biol.* 2017, 27, 126–140. [CrossRef]

30. Goto, H.; Inoko, A.; Inagaki, M. Cell cycle progression by the repression of primary cilia formation in proliferating cells. *Cell. Mol. Life Sci.* CMLS 2013, 70, 3893–3905. [CrossRef]

31. Izawa, I.; Goto, H.; Kasahara, K.; Inagaki, M. Current topics of functional links between primary cilium and cell cycle. *Cilia* 2015, 4, 12. [CrossRef] [PubMed]

32. Goto, H.; Inaba, H.; Inagaki, M. Mechanisms of ciliogenesis suppression in dividing cells. *Cell. Mol. Life Sci.* CMLS 2017, 74, 881–890. [CrossRef]

33. Nishimura, Y.; Kasahara, K.; Shiromizu, T.; Watanabe, M.; Inagaki, M. Primary cilia as signaling hubs in health and disease. *Adv. Sci.* 2019, 6, 1801138. [CrossRef] [PubMed]

34. Kasahara, K.; Inagaki, M. Primary ciliary signaling: Links with the cell cycle. *Trends Cell Biol.* 2021, 31, 954–964. [CrossRef]

35. Garcia, G.; Raleigh, D.R.; Reiter, J.F. How the Ciliary Membrane Is Organized Inside-Out to Communicate Outside-In. *Curr. Biol.* 2018, 28, R421–R434. [CrossRef] [PubMed]

36. Elliott, K.H.; Brugmann, S.A. Sending mixed signals: Cilia-dependent signaling during development and disease. *Dev. Biol.* 2018, 447, 28–41. [CrossRef] [PubMed]

37. Wang, L.; Dynlacht, B.D. The regulation of cilium assembly and disassembly in development and disease. *Development* 2018, 145. [CrossRef] [PubMed]

38. Nishimura, Y.; Kasahara, K.; Inagaki, M. Intermediate filaments and IF-associated proteins: From cell architecture to cell proliferation. *Proc. Jpn. Acad. Ser. B Phys. Biol. Sci.* 2019, 95, 479–493. [CrossRef]

39. Bernabé-Rubio, M.; Alonso, M.A. Routes and machinery of primary cilium biogenesis. *Cell. Mol. Life Sci.* 2017, 74, 4077–4095. [CrossRef]

40. Mirvis, M.; Stearns, T.; James Nelson, W. Cilium structure, assembly, and disassembly regulated by the cytoskeleton. *Biochem. J.* 2018, 475, 2329–2335. [CrossRef]

41. Hossain, D.; Tsang, W.Y. The role of ubiquitination in the regulation of primary cilium assembly and disassembly. *Semin. Cell Dev. Biol.* 2019, 93, 145–152. [CrossRef] [PubMed]

42. Wang, B.; Liang, Z.; Liu, P. Functional aspects of primary cilium in signaling, assembly and microenvironment in cancer. *J. Cell. Physiol.* 2021, 236, 3207–3219. [CrossRef] [PubMed]

43. Tucker, R.W.; Pardeeb, A.B.; Fujiwara, K. Centriole ciliation is related to quiescence and DNA synthesis in 3T3 cells. *Cell 1979*, 17, 527–535. [CrossRef]
44. Tucker, R.W.; Scher, C.D.; Stiles, C.D. Centriole deciliation associated with the early response of 3T3 cells to growth factors but not to SV40. *Cell* **1979**, *18*, 1065–1072. [CrossRef]

45. Rieder, C.L.; Jensen, C.G.; Jensen, L.C.W. The resorption of primary cilia during mitosis in a vertebrate (PtK1) cell line. *J. Ultrastruct. Res.* **1979**, *68*, 173–185. [CrossRef]

46. Puga-Cheva, E.N.; Jablonski, S.A.; Hartman, T.R.; Henske, E.P.; Golemis, E.A. HEF1-dependent Aurora A activation induces disassembly of the primary cilium. *Cell* **2007**, *129*, 1351–1363. [CrossRef]

47. Inaba, H.; Goto, H.; Kasahara, K.; Kumamoto, K.; Yonemura, S.; Hoshi, A.; Yamano, S.; Wanibuchi, H.; He, D.; Goshima, N.; et al. Nedd1 suppresses ciliogenesis in proliferating cells by regulating the trichoplein-Aurora A pathway. *J. Cell Biol.* **2012**, *197*, 391–405. [CrossRef]

48. Kasahara, K.; Kawakami, Y.; Kiyono, T.; Yonemura, S.; Kawamura, Y.; Era, S.; Matsuzaki, F.; Goshima, N.; et al. Ubiquitin-proteasome system controls ciliogenesis at the initial step of axoneme extension. *Nat. Commun.* **2014**, *5*, 5081. [CrossRef]

49. Inaba, H.; Goto, H.; Kasahara, K.; Kumamoto, K.; Yonemura, S.; Inoko, A.; Yamano, S.; Wanibuchi, H.; He, D.; Goshima, N.; et al. Trichoplein and Aurora A block aberrant primary cilia assembly in proliferating cells. *J. Cell Biol.* **2012**, *197*, 391–405. [CrossRef]

50. Kasahara, K.; Aoki, H.; Kiyono, T.; Wang, S.; Kagiwada, H.; Yuge, M.; Tanaka, T.; Nishimura, Y.; Mizoguchi, A.; Goshima, N.; et al. EGFR receptor kinase suppresses ciliogenesis through activation of USP8 deubiquitinase. *Nat. Commun.* **2018**, *9*, 758. [CrossRef]

51. Urdicliaia, A.; Erausquin, E.; Meléndez, B.; Rey, J.A.; Idone, P.A.; Castresana, J.S. Tubastatin A, an inhibitor of HDAC6, enhances temozolomide-induced apoptosis and reverses the malignant phenotype of glioblastoma cells. *Int. J. Oncol.* **2019**, *54*, 1797–1808. [CrossRef] [PubMed]

52. Chen, Q.; Li, J.; Yang, X.; Li, J.; Liu, Y. Prdx1 promotes the loss of primary cilia in esophageal squamous cell carcinoma. *BMC Cancer* **2020**, *20*, 372. [CrossRef] [PubMed]

53. Rocha, C.; Papon, L.; Cacheux, W.; Marques Sousa, P.; Lascano, V.; Tort, O.; Giordano, T.; Vacher, S.; Lemmers, B.; Mariani, P.; et al. Tubulin glycolases are required for primary cilia, control of cell proliferation and tumor development in colon. *EMBO J.* **2014**, *33*, 2247–2260. [CrossRef]

54. Gradilone, S.A.; Radtke, B.N.; Bogert, P.S.; Huang, B.Q.; Gajdos, G.B.; LaRusso, N.F. HDAC6 inhibition restores ciliary expression and decreases tumor growth. *Cancer Res.* **2013**, *73*, 2259–2270. [CrossRef] [PubMed]

55. Mansini, A.P.; Peixoto, E.; Thelen, K.M.; Gaspari, C.; Jin, S.; Gradilone, S.A. The cholangiocyte primary cilium in health and disease. *Biochim. Biophys. Acta* **2018**, *1864*, 1245–1253. [CrossRef] [PubMed]

56. Seeley, E.S.; Carriere, C.; Goetze, T.; Longnecker, D.S.; Korc, M. Pancreatic cancer and precursor pancreatic intraepithelial neoplasia lesions are devoid of primary cilia. *Cancer Res.* **2009**, *69*, 422–430. [CrossRef]

57. Kobayashi, T.; Nakazono, K.; Tokuda, M.; Mochida, Y.; Dymlacht, B.D.; Itoh, H. HDAC2 promotes loss of primary cilia in pancreatic ductal adenocarcinoma. *EMBO Rep.* **2017**, *18*, 334–343. [CrossRef] [PubMed]

58. Esteban, M.A.; Harten, S.K.; Tran, M.G.; Maxwell, P.H. Formation of primary cilia in the renal epithelium is regulated by the von Hippel-Lindau tumor suppressor protein. *J. Am. Soc. Nephrol.* **2006**, *17*, 1801–1806. [CrossRef] [PubMed]

59. Schraml, P.; Frew, I.J.; Thoma, C.R.; Boysen, G.; Struckmann, K.; Kreck, W.; Moch, H. Sporadic clear cell renal cell carcinomas versus neighboring parenchymal tissue. *Mod. Pathol.* **2009**, *22*, 173–185. [CrossRef] [PubMed]

60. Basten, S.G.; Willekers, S.; Vermaat, J.S.; Sluiter, B.; van Diest, P.; et al. The resorption of primary cilia during mitosis in a vertebrate (PtK1) cell line. *J. Cell Biol.* **2009**, *186*, 7659–7666. [CrossRef] [PubMed]

61. Dere, R.; Perkins, A.L.; Bawa-Khalfe, T.; Jonasch, D.; Walker, C.L.; et al. Trichoplein and Aurora A block aberrant primary cilia assembly in proliferating cells. *J. Cell Biol.* **2012**, *197*, 391–405. [CrossRef]

62. Bhattacharya, R.; Kwon, J.; Ali, B.; Wang, E.; Patra, S.; Shridhar, V.; Mukherjee, P. Role of hedgehog signaling in ovarian cancer. *Clin. Cancer Res.* **2008**, *14*, 7659–7666. [CrossRef] [PubMed]

63. Eggerberg, D.L.; Lethan, M.; Mansurov, R.; Schneider, L.; Anwan, A.; Jorgensen, T.S.; Byskov, A.G.; Pedersen, L.B.; Christensen, S.T. Primary cilia and aberrant cell signaling in epithelial ovarian cancer. *Cilia* **2012**, *1*, 15. [CrossRef]

64. Yuan, K.; Frolova, N.; Xie, Y.; Wang, D.; Cook, L.; Kwon, Y.J.; Steg, A.D.; Serra, R.; Frost, A.R. Primary cilia are decreased in breast cancer: Analysis of a collection of human breast cancer cell lines and tissues. *Histochem. Cytochem.* **2010**, *58*, 857–870. [CrossRef] [PubMed]

65. Hassounah, N.B.; Nagle, R.; Saboda, K.; Roe, D.J.; Dalkin, B.L.; McDermott, K.M. Primary cilia are lost in preinvasive and invasive prostate cancer. *PLoS ONE* **2013**, *8*, e66821. [CrossRef] [PubMed]

66. Qie, Y.; Wang, L.; Du, E.; Chen, S.; Lu, C.; Ding, N.; Yang, K.; Xu, Y. TACC3 promotes prostate cancer cell proliferation and restrains primary cilium formation. *Exp. Cell Res.* **2020**, *390*, 111952. [CrossRef] [PubMed]

67. Kim, J.; Dabiri, S.; Seeley, E.S. Primary cilium depletion typifies cutaneous melanoma in situ and malignant melanoma. *PLoS ONE* **2011**, *6*, e27410. [CrossRef] [PubMed]

68. Zingg, D.; Debbache, J.; Peña-Hernández, R.; Antunes, A.T.; Schaefer, S.M.; Cheng, P.F.; Zimmerman, D.; Haeusel, J.; Calçada, R.R.; Tuncer, E.; et al. EZH2-Mediated Primary Cilium Deconstruction Drives Metastatic Melanoma Formation. *Cancer Cell* **2018**, *34*, 69–84. [CrossRef]

69. Ho, L.; Ali, S.A.; Al-Jazrawe, M.; Kandel, R.; Wunder, J.S.; Alman, B.A. Primary cilia attenuate hedgehog signalling in neoplastic chondrocytes. *Oncogene* **2013**, *32*, 5388–5396. [CrossRef]
70. Xiang, W.; Guo, F.; Cheng, W.; Zhang, J.; Huang, J.; Wang, R.; Ma, Z.; Xu, K. HDAC6 inhibition suppresses chondrosarcoma by restoring the expression of primary cilia. Oncol. Rep. 2017, 38, 229–236. [CrossRef]

71. Liu, H.; Kiseleva, A.A.; Golemis, E.A. Ciliary signalling in cancer. Nat. Rev. Cancer 2018, 18, 511–524. [CrossRef]

72. Fabbri, L.; Bost, F.; Mazure, N.M. Primary Cilium in Cancer Hallmarks. Int. J. Mol. Sci. 2019, 20, 1336. [CrossRef]

73. Higgins, M.; Obaidi, I.; McMorrow, T. Primary cilia and their role in cancer. Oncol. Lett. 2019, 17, 3041–3047. [CrossRef] [PubMed]

74. Shirromizu, T.; Yuge, M.; Kasahara, K.; Yamakawa, D.; Matsu, T.; Bessho, Y.; Inagaki, M.; Nishimura, Y. Targeting E3 Ubiquitin Ligases and Deubiquitinases in Ciliopathy and Cancer. Int. J. Mol. Sci. 2020, 21, 5962. [CrossRef]

75. Peixoto, E.; Richard, S.; Pant, K.; Blasw, A.; Gradilone, S.A. The primary cilium: Its role as a tumor suppressor organelle. Biochem. Pharm. 2020, 175, 115906. [CrossRef] [PubMed]

76. Helder, P.; Khatun, S.; Majumder, S. Freeing the brake: Proliferation needs primary cilium to disassemble. J. Biosci. 2020, 45. [CrossRef]

77. Mariman, E.C.; Vink, R.G.; Roumans, N.J.; Bouwman, F.G.; Stumpel, C.T.; Aller, E.E.; van Baak, M.A.; Wang, P. The cilium: A cellular antenna with an influence on obesity risk. Br. J. Nutr. 2016, 116, 576–592. [CrossRef]

78. Hilgendorf, K.I.; Johnson, C.T.; Mezger, A.; Rice, S.L.; Norris, A.M.; Demeter, J.; Greenleaf, W.J.; Reiter, J.F.; Kopinke, D.; Jackson, P.K. Omega-3 Fatty Acids Activate Ciliary FFAR4 to Control Adipogenesis. Cell 2019, 179, 1289–1305.e1221. [CrossRef]

79. Yamakawa, D.; Katoh, D.; Kasahara, K.; Shiromizu, T.; Matsuyama, M.; Matsu, C.; Maeno, Y.; Watanabe, M.; Nishimura, Y.; Inagaki, M. Primary cilia-dependent lipid raft/caveolin dynamics regulate adipogenesis. Cell Rep. 2021, 34, 108817. [CrossRef] [PubMed]

80. Han, Y.M.; Kang, G.M.; Byun, K.; Ko, H.W.; Kim, J.; Shin, M.S.; Kim, H.; Gil, S.Y.; Yu, J.H.; Lee, B.; et al. Leptin-promoted cilia assembly is critical for normal energy balance. J. Clin. Investig. 2014, 124, 2193–2197. [CrossRef] [PubMed]

81. Ernst, M.B.; Wunderlich, C.M.; Hess, S.; Paehler, M.; Mesaros, A.; Koralov, S.B.; Kleinridders, A.; Husch, A.; Munzberg, H.; Hampel, B.; et al. Enhanced Stat3 activation in POMC neurons provokes negative feedback inhibition of leptin and insulin signaling in obesity. J. Neurosci. 2009, 29, 11582–11593. [CrossRef] [PubMed]

82. Mesaros, A.; Koralov, S.B.; Rother, E.; Wunderlich, F.T.; Ernst, M.B.; Barsh, G.S.; Rajewsky, K.; Bruning, J.C. Activation of Stat3 signaling in AgRP neurons promotes locomotor activity. Cell Metab. 2008, 7, 236–248. [CrossRef] [PubMed]

83. Davenport, J.R.; Watts, A.J.; Roper, V.C.; Croyle, M.J.; van Groen, T.; Wyss, J.M.; Nagy, T.R.; Kesterson, R.A.; Yoder, B.K. Disruption of intraflagellar transport in adult mice leads to obesity and slow-onset cystic kidney disease. Curr. Biol. 2007, 17, 1586–1594. [CrossRef]

84. Oh, E.C.; Vasanth, S.; Katsanis, N. Metabolic regulation and energy homeostasis through the primary Cilium. Cell Metab. 2015, 21, 21–31. [CrossRef]

85. Siljee, J.E.; Wang, Y.; Bernard, A.A.; Ersoy, B.A.; Zhang, S.; Marley, A.; Von Zastrow, M.; Reiter, J.F.; Vaisse, C. Subcellular localization of MC4R with ADCY3 at neuronal primary cilia underlies a common pathway for genetic predisposition to obesity. Nat. Genet. 2018, 50, 180–185. [CrossRef]

86. Grarup, N.; Moltke, I.; Andersen, M.K.; Dahl-Petersen, I.K.; Dalby, M.; Vitting-Seerup, K.; Kern, T.; Mahendran, Y.; Jorsboe, E.; Larsen, C.V.L.; Dahl-Petersen, I.K.; et al. Loss-of-function variants in ADCY3 increase risk of obesity and type 2 diabetes. Nat. Genet. 2018, 50, 172–174. [CrossRef]

87. Saeed, S.; Bonnefond, A.; Tamanini, F.; Mirza, M.U.; Manzoor, J.; Janjua, Q.M.; Din, S.M.; Gaitan, J.; Milochau, A.; Durand, E.; et al. Loss-of-function mutations in ADCY3 cause monogenic severe obesity. Nat. Genet. 2018, 50, 175–179. [CrossRef]

88. Loos, R.J.; Lindgren, C.M.; Li, S.; Wheel, E.; Zhao, J.H.; Prokopenko, I.; Inouye, M.; Freathy, R.M.; Attwood, A.P.; Beckmann, J.S.; et al. Common variants near MC4R are associated with fat mass, weight and risk of obesity. Nat. Genet. 2018, 50, 768–775. [CrossRef]

89. Sebo, Z.L.; Rodeheffer, M.S. Assembling the adipose organ: Adipocyte lineage segregation and adipogenesis in vivo. Development 2019, 146. [CrossRef] [PubMed]

90. Marcon, V.; Stoeztel, C.; Schlicht, D.; Messaddeq, N.; Koch, M.; Flori, E.; Danse, J.M.; Mandel, J.L.; Dollfus, H. Transient ciliogenesis involving Bardet-Biedl syndrome proteins is a fundamental characteristic of adiogenic differentiation. Proc. Natl. Acad. Sci. USA 2009, 106, 1820–1825. [CrossRef]

91. Marcon, V.; Mockel, A.; De Melo, C.; Obringer, C.; Claussmann, A.; Simon, A.; Messadeg, N.; Durand, M.; Dupuis, L.; Loeffler, J.P.; et al. BBS-induced ciliary defect enhances adipogenesis, causing paradoxical higher-insulin sensitivity, glucose usage, and decreased inflammatory response. Cell Metab. 2012, 16, 363–377. [CrossRef]

92. Conduit, S.E.; Vanhaesebroeck, B. Phosphoinositide lipids in primary cilia biology. Biochem. J. 2020, 477, 3541–3565. [CrossRef] [PubMed]

93. Jokels, A.; Viey, S.; Wong, P.; Kostaras, E.; Keller, D.; Burgooyne, T.; Shoemaker, A.; Tsalikis, A.; de la Roche, M.; Michaelis, M.; et al. Primary Cilia Mediate Diverse Kinase Inhibitor Resistance Mechanisms in Cancer. Cell Rep. 2018, 23, 3042–3055. [CrossRef]

94. Ritter, A.; Kreis, N.N.; Roth, S.; Friemel, A.; Jennewein, L.; Eichbaum, C.; Solbach, C.; Louwen, F.; Yuan, J. Restoration of primary cilia in obese adipose-derived mesenchymal stem cells by inhibiting Aurora A or extracellular signal-regulated kinase. Stem Cell Res. Ther. 2019, 10, 255. [CrossRef]

95. Carmena, M.; Earnshaw, W.C.; Glover, D.M. The Dawn of Aurora Kinase Research: From Fly Genetics to the Clinic. Front. Cell Dev. Biol. 2015, 3. [CrossRef] [PubMed]
96. Otto, T.; Sicinski, P. Cell cycle proteins as promising targets in cancer therapy. Nat. Rev. Cancer 2017, 17, 93–115. [CrossRef]
97. Nikonova, A.S.; Assisaturou, I.; Serebriiskii, I.G.; Dunbrack, R.L.; Golemis, E.A. Aurora A kinase (AURKA) in normal and pathological cell division. Cell. Mol. Life Sci. CMLS 2013, 70, 661–687. [CrossRef] [PubMed]
98. Mardin, B.R.; Schiebel, E. Breaking the ties that bind: New advances in centrosome biology. J. Cell Biol. 2012, 197, 11–18. [CrossRef] [PubMed]
99. Mardin, B.R.; Agircan, F.G.; Lange, C.; Schiebel, E. Plk1 controls the Nek2A-PP1γ antagonism in centrosome disjunction. Curr. Biol. 2011, 21, 1145–1151. [CrossRef]
100. Hutterer, A.; Berndik, D.; Wirtz-Peitz, F.; Zigman, M.; Schleiffer, A.; Knoblich, J.A. Mitotic activation of the kinase Aurora-A requires its binding partner Bora. Dev. Cell 2006, 11, 147–157. [CrossRef]
101. Hirota, T.; Kunitokou, N.; Sasayama, T.; Marumoto, T.; Zhang, D.; Nitta, M.; Hatakeyama, K.; Saya, H. Aurora-A and an Interacting Activator, the LIM Protein Auba, Are Required for Mitotic Commitment in Human Cells. Cell 2003, 114, 585–598. [CrossRef]
102. Giubettini, M.; Asteriti, I.A.; Scrofani, J.; De Luca, M.; Lindon, C.; Lavia, P.; Guarguaglini, G. Control of Aurora-A stability through interaction with TPX2. J. Cell Sci. 2011, 124, 113–122. [CrossRef]
103. Tsai, M.-Y.; Zheng, Y. Aurora A Kinase-Coated Beads Function as Microtubule-Organizing Centers and Enhance RanGTP-Induced Spindle Assembly. Curr. Biol. 2005, 15, 2156–2163. [CrossRef]
104. Sasai, K.; Parant, J.M.; Brandt, M.E.; Carter, J.; Adams, H.P.; Stass, S.A.; Killary, A.M.; Katayama, H.; Sen, S. Targeted disruption of Aurora A causes abnormal mitotic spindle assembly, chromosome misalignment and embryonic lethality. Oncogene 2008, 27, 4122–4127. [CrossRef] [PubMed]
105. Plotnikova, O.V.; Nikonova, A.S.; Loskutov, Y.V.; Kozyulina, P.Y.; Pugacheva, E.N.; Golemis, E.A. Calmodulin activation of Aurora-A kinase (AURKA) is required during ciliary disassembly and in mitosis. Mol. Biol. Cell 2012, 23, 2658–2670. [CrossRef]
106. Lee, K.H.; Johmura, Y.; Yu, L.R.; Park, J.E.; Gao, Y.; Bang, J.K.; Zhou, M.; Veenstra, T.D.; Yeon Kim, B.; Lee, K.S. Identification of a novel Wnt5α-CK1varepsilon-Dvl2-Plk1-mediated primary cilia disassembly pathway. EMBO J. 2012, 31, 3104–3117. [CrossRef]
107. Li, D.; Zhu, J.; Firozi, P.F.; Abbruzzese, J.L.; Evans, D.B.; Cleary, K.; Friess, H.; Sen, S. Overexpression of oncogenic STK15/βTAK/Aurora A kinase in human pancreatic cancer. Clin. Cancer Res. 2003, 9, 991–997. [PubMed]
108. Duncan, C.G.; Killela, P.J.; Payne, C.A.; Lampson, B.; Chen, W.C.; Liu, J.; Solomon, D.; Waldman, T.; Towers, A.J.; Gregory, S.G.; et al. Integrated genomic analyses identify ERRFI1 and TAC3 as glioblastoma-targeted genes. Oncotarget 2010, 1, 265–277. [CrossRef] [PubMed]
109. Álvarez-Satta, M.; Matheu, A. Primary cilium and glioblastoma. Adv. Med. Oncol. 2018, 10. [CrossRef]
110. Nishizawa, M.; Izawa, I.; Inoko, A.; Hayashi, Y.; Nagata, K.; Yokoyama, T.; Usukura, J.; Inagaki, M. Identification of trichopelin, a novel keratin filament-binding protein. J. Cell Sci. 2005, 118, 1081–1090. [CrossRef] [PubMed]
111. Ibi, M.; Zou, P.; Inoko, A.; Shiromizu, T.; Matsuyama, M.; Hayashi, Y.; Enomoto, M.; Mori, D.; Hirotsune, S.; Kiyono, T.; et al. Trichopelin controls microtubule anchoring at the centrosome by binding to Odf2 and ninein. J. Cell Sci. 2011, 124, 857–864. [CrossRef] [PubMed]
112. Zhou, M.H.; Lin, Y.; Zhang, Z.G. Intraflagellar transport 20: New target for the treatment of ciliopathies. Biochem. Biophys. Acta Mol. Cell Res. 2020, 1867, 118641. [CrossRef]
113. Kinzel, D.; Boldt, K.; Davis, E.E.; Burtcher, I.; Trümbach, D.; Diplas, B.; Attié-Bitach, T.; Wurst, W.; Katsanis, N.; Ueffing, M.; et al. Pitchfork regulates primary cilia disassembly and left-right asymmetry. Dev. Cell 2010, 19, 66–77. [CrossRef] [PubMed]
114. Nikonova, A.S.; Deneka, A.Y.; Kiseleva, A.A.; Korobeynikov, V.; Gaponova, A.; Serebriiskii, I.G.; Kop, M.C.; Hensley, H.H.; Seeger-Nukpezah, T.N.; Somlo, S.; et al. Granetespib limits ciliation and cystogenesis in autosomal-dominant polycystic kidney disease (ADPKD). FASEB J. 2018, 32, 2735–2746. [CrossRef] [PubMed]
115. Sasaki, S.; Shionoya, A.; Ishida, M.; Gambello, M.J.; Yingling, J.; Wynshaw-Boris, A.; Hirotsune, S. A LIS1/NUDEL/cytoplasmic dynein heavy chain complex in the developing and adult nervous system. Neuron 2000, 28, 681–696. [CrossRef]
116. Niethermmer, M.; Smith, D.S.; Ayala, R.; Peng, J.; Ko, J.; Lee, M.S.; Morabito, M.; Tsai, L.H. NUDEL is a novel Cdk5 substrate that associates with LIS1 and cytoplasmic dynein. Neurophin 2000, 28, 673–711. [CrossRef]
117. Pugacheva, E.N.; Golemis, E.A. The focal adhesion scaffolding protein HEF1 regulates activation of the Aurora-A and Nek2 kinases at the centrosome. Nat. Cell Biol. 2005, 7, 937–946. [CrossRef] [PubMed]
118. Ice, R.J.; McLaughlin, S.L.; Livengood, R.H.; Culp, M.V.; Eddy, E.R.; Ivanov, A.V.; Pugacheva, E.N. NEDD9 depletion destabilizes Aurora A kinase and heightens the efficacy of Aurora A inhibitors: Implications for treatment of metastatic solid tumors. Cancer Res. 2013, 73, 3168–3180. [CrossRef]
119. Plotnikova, O.V.; Pugacheva, E.N.; Dunbrack, R.L.; Golemis, E.A. Rapid calcium-dependent activation of Aurora-A kinase. Nat. Commun. 2010, 1, 1–8. [CrossRef] [PubMed]
120. Ding, C.; Fan, X.; Wu, G. Peroxiredoxin 1—an antioxidant enzyme in cancer. J. Cell Mol. Med. 2017, 21, 193–202. [CrossRef] [PubMed]
121. Ledgerwood, E.C.; Marshall, J.W.; Weijman, J.F. The role of peroxiredoxin 1 in redox sensing and transducing. Arch. Biochem. Biophys. 2017, 617, 60–67. [CrossRef] [PubMed]
122. Shagisultanova, E.; Gaponova, A.V.; Gabbasov, R.; Nicolas, E.; Golemis, E.A. Preclinical and clinical studies of the NEDD9 scaffold protein in cancer and other diseases. Gene 2015, 567, 1–11. [CrossRef] [PubMed]
123. Nikonova, A.S.; Plotnikova, O.V.; Serzhanova, V.; Efimov, A.; Bogush, I.; Cai, K.Q.; Hensley, H.H.; Egleston, B.L.; Klein-Szanto, A.; Seeger-Nukpezah, T.; et al. Nedd9 restrains renal cystogenesis in Pkd1−/− mice. *Proc. Natl. Acad. Sci. USA* 2014, 111, 12859–12864. [CrossRef]

124. Riazuddin, S.A.; Iqbal, M.; Wang, Y.; Masuda, T.; Chen, Y.; Bowne, S.; Sullivan, L.S.; Waseem, N.H.; Bhattacharya, S.; Daiger, S.P.; et al. A splice-site mutation in a retina-specific exon of BBS8 causes nonsyndromic retinitis pigmentosa. *Am. J. Hum. Genet.* 2010, 86, 805–812. [CrossRef] [PubMed]

125. Goyal, S.; Jäger, M.; Robinson, P.N.; Vanita, V. Confirmation of TTC8 as a disease gene for nonsyndromic autosomal recessive retinitis pigmentosa (RP51). *Clin. Genet.* 2016, 89, 454–460. [CrossRef] [PubMed]

126. May-Simera, H.L.; Wan, Q.; Jha, B.S.; Hartford, J.; Khristov, V.; Dejene, R.; Chang, J.; Patnaik, S.; Lu, Q.; Banerjee, P.; et al. Primary cilium-mediated retinal pigment epithelium maturation is disrupted in ciliopathy patient cells. *Cell Rep.* 2018, 22, 189–205. [CrossRef] [PubMed]

127. Ansley, S.J.; Badano, J.L.; Blacque, O.E.; Hill, J.; Hoskins, B.E.; Leitch, C.C.; Kim, J.C.; Ross, A.J.; Eichers, E.R.; Teslovich, T.M.; et al. Basal body dysfunction is a likely cause of pleiotropic Bardet-Biedl syndrome. *Nature* 2003, 425, 628–633. [CrossRef] [PubMed]

128. Patnaik, S.R.; Kretschmer, V.; Brücker, L.; Schneider, S.; Volz, A.K.; Oancea-Castillo, L.D.R.; May-Simera, H.L. Bardet-Biedl Syndrome proteins regulate cilia disassembly during tissue maturation. *Cell Mol. Life Sci.* 2019, 76, 757–775. [CrossRef] [PubMed]

129. Frosk, P.; Arts, H.H.; Philippe, J.; Gunn, C.S.; Brown, E.L.; Chodorir, B.; Simard, L.; Majewski, J.; Fahimiyya, S.; Russell, C.; et al. A truncating mutation in CEP55 is the likely cause of MARCH, a novel syndrome affecting neuronal mitosis. *J. Med. Genet.* 2017, 54, 490–501. [CrossRef] [PubMed]

130. Bondeson, M.L.; Ericson, K.; Gudmundsson, S.; Ameer, A.; Pontén, F.; Wesström, J.; Frykholm, C.; Wilbe, M. A nonsense mutation in CEP55 defines a new locus for a Meckel-like syndrome, an autosomal recessive lethal fetal ciliopathy. *Clin. Genet.* 2017, 92, 510–516. [CrossRef] [PubMed]

131. Rawlins, L.E.; Jones, H.; Wenger, O.; Aye, M.; Fasham, J.; Harlalka, G.V.; Chioza, B.A.; Miron, A.; Ellard, S.; Wakeling, M.; et al. An Amish founder variant consolidates disruption of CEP55 as a cause of hydranencephaly and renal dysplasia. *Eur. J. Hum. Genet.* 2019, 27, 657–662. [CrossRef]

132. Zhang, Y.-C.; Bai, Y.-F.; Yuan, J.-F.; Shen, X.-L.; Xu, Y.-L.; Jian, X.-X.; Li, S.; Song, Z.-Q.; Hu, H.-B.; Li, P.-Y.; et al. CEP55 promotes cilia disassembly through stabilizing Aurora A kinase. *J. Cell Biol.* 2021, 220. [CrossRef] [PubMed]

133. Wang, G.; Liu, M.; Wang, H.; Yu, S.; Jiang, Z.; Sun, J.; Han, K.; Shen, J.; Zhu, M.; Lin, Z.; et al. Centrosomal Protein of 55 Regulates Glucose Metabolism, Proliferation and Apoptosis of Glioma Cells via the Akt/mTOR Signaling Pathway. *J. Cancer* 2016, 7, 1431–1440. [CrossRef] [PubMed]

134. Zhu, H.; Chen, D.; Tang, J.; Huang, C.; Lv, S.; Wang, D.; Li, G. Overexpression of centrosomal protein 55 regulates the proliferation of glioma cell and mediates proliferation promoted by EGFRvIII in glioblastoma U251 cells. *Oncol. Lett.* 2018, 15, 2700–2706. [CrossRef]

135. Margaria, J.P.; Campa, C.C.; De Santis, M.C.; Hirsch, E.; Franco, I. The PI3K/Akt/mTOR pathway in polycystic kidney disease: A complex interaction with polycystins and primary ciliary. *Cell Signal.* 2020, 66, 109468. [CrossRef] [PubMed]

136. Manning, B.D.; Toker, A. AKT/PKB Signaling: Navigating the Network. *Cell* 2017, 169, 381–405. [CrossRef] [PubMed]

137. Thoma, C.R.; Frew, I.J.; Hoerner, C.R.; Montani, M.; Moch, H.; Krek, W. pVHL and GSK3beta are components of a primary cilium-maintenance signalling network. *Nat. Cell Biol.* 2007, 9, 588–595. [CrossRef] [PubMed]

138. Beurel, E.; Grieco, S.F.; Jope, R.S. Glycogen synthase kinase-3 (GSK3): Regulation, actions, and diseases. *Pharmacol. Ther.* 2015, 148, 114–131. [CrossRef]

139. Gao, X.; Lowry, P.R.; Zhou, X.; Depry, C.; Wei, Z.; Wong, G.W.; Zhang. J. PI3K/Akt signaling requires spatial compartmentalization in plasma membrane microdomains. *Proc. Natl. Acad. Sci. USA* 2011, 108, 14509–14514. [CrossRef] [PubMed]

140. Guo, J.; Otis, J.M.; Suciu, S.K.; Catalano, C.; Xing, L.; Constable, S.; Wachten, D.; Gupton, S.; Lee, J.; Lee, A.; et al. Primary Cilia Signaling Promotes Axonal Tract Development and Is Disrupted in Joubert Syndrome-Related Disorders Models. *Dev. Cell* 2019, 51, 759–774.e755. [CrossRef] [PubMed]

141. Forcioli-Conti, N.; Lacas-Gervais, S.; Dani, C.; Peraldi, P. The primary cilium undergoes dynamic size modifications during tissue maturation. *Semin. Cell Dev. Biol.* 2015, 381–405. [CrossRef] [PubMed]

142. Zhu, D.; Shi, S.; Wang, H.; Liao, K. Growth arrest induces primary-cilium formation and sensitizes IGF-1-receptor signaling during differentiation induction of 3T3-L1 preadipocytes. *J. Cell Sci.* 2009, 122, 2760–2768. [CrossRef] [PubMed]

143. Dalbay, M.T.; Thorpe, S.D.; Connelly, J.T.; Chapelle, J.P.; Knight, M.M. Adipogenic Differentiation of hMSCs is Mediated by Recruitment of IGF-1R On to the Primary Cilium Associated With Cilia Elongation. *Stem Cells* 2015, 33, 1952–1961. [CrossRef]

144. Haczyzyni, F.; Bell-Anderson, K.S.; Farrell, G.C. Causes and mechanisms of adipocyte enlargement and adipose expansion. *Obes. Rev.* 2018, 19, 406–420. [CrossRef] [PubMed]

145. Kopinke, D.; Roberson, E.C.; Reiter, J.F. Ciliary Hedgehog Signaling Restricts Injury-Induced Adipogenesis. *Cell* 2017, 170, 340–351. [CrossRef] [PubMed]

146. Huo, H.; Guo, X.; Hong, S.; Jiang, M.; Liu, X.; Liao, K. Lipid rafts/caveolae are essential for insulin-like growth factor-1 receptor signaling during 3T3-L1 preadipocyte differentiation induction. *J. Biol. Chem.* 2003, 278, 11561–11569. [CrossRef]
148. Sánchez-Wandelmer, J.; Dávalos, A.; Herrera, E.; Giera, M.; Cano, S.; de la Peña, G.; Lasunción, M.A.; Busto, R. Inhibition of cholesterol biosynthesis disrupts lipid raft/caveolae and affects insulin receptor activation in 3T3-L1 preadipocytes. *Biochim. Biophys. Acta* **2009**, *1788*, 1731–1739. [CrossRef]

149. Levental, I.; Levental, K.R.; Heberle, F.A. Lipid Rafts: Controversies Resolved, Mysteries Remain. *Trends Cell Biol.* **2020**, *30*, 341–353. [CrossRef]

150. Sezgin, E.; Levental, I.; Mayor, S.; Eggeling, C. The mystery of membrane organization: Composition, regulation and roles of lipid rafts. *Nat. Rev. Mol. Cell Biol.* **2017**, *18*, 361–374. [CrossRef]

151. Van Deventer, S.; Arp, A.B.; van Spriel, A.B. Identification of filamin as a novel ligand for caveolin-1: Evidence for the organization of caveolin-1-associated membrane domains by the actin cytoskeleton. *Mol. Biol. Cell* **2000**, *11*, 325–337. [CrossRef]

152. Pike, L.J. Lipid rafts as major platforms for signaling regulation in cancer. *Adv. Biol. Regul.* **2013**, *57*, 130–146. [CrossRef] [PubMed]

153. Mollinedo, F.; Gajate, C. Lipid rafts as signaling hubs in cancer cell survival/death and invasion: Implications in tumor progression and therapy. *J. Lipid. Res.* **2020**, *61*, 611–635. [CrossRef] [PubMed]

154. Nishimura, Y.; Yamakawa, D.; Uchida, K.; Shiromizu, T.; Watanabe, M.; Inagaki, M. Primary cilia and lipid raft dynamics. *J. Lipid. Res.* **2011**, *52*, 145–154. [CrossRef] [PubMed]

155. Nishimura, Y.; Yamakawa, D.; Uchida, K.; Shiromizu, T.; Watanabe, M.; Inagaki, M. Primary cilia and lipid raft dynamics. *J. Lipid. Res.* **2011**, *52*, 145–154. [CrossRef] [PubMed]

156. Beloribi-Djefaflia, S.; Vasseur, S.; Guillaumond, F. Lipid metabolic reprogramming in cancer cells. *Biochim. Biophys. Acta* **2015**, *1853*, 3707–3721. [CrossRef] [PubMed]

157. Beloribi-Djefaflia, S.; Vasseur, S.; Guillaumond, F. Lipid metabolic reprogramming in cancer cells. *Biochim. Biophys. Acta* **2015**, *1853*, 3707–3721. [CrossRef] [PubMed]

158. Pike, L.J. Rafts defined: A report on the Keystone Symposium on Lipid Rafts and Cell Function. *Adv. Biol. Regul.* **2011**, *51*, 273–297. [CrossRef] [PubMed]

159. Pike, L.J. Rafts defined: A report on the Keystone Symposium on Lipid Rafts and Cell Function. *Adv. Biol. Regul.* **2011**, *51*, 273–297. [CrossRef] [PubMed]

160. Lu, S.M.; Fairn, G.D. Mesoscale organization of domains in the plasma membrane—Beyond the lipid raft. *Front. Cell Dev. Biol.* **2020**, *8*, 119–129. [CrossRef] [PubMed]

161. Choudhury, A.; Neumann, N.M.; Raleigh, D.R.; Lang, U.E. Clinical Implications of Primary Cilia in Skin Cancer. *Dermatol. Ther.* **2020**, *13*, 233–248. [CrossRef] [PubMed]

162. Eramo, M.J.; Mitchell, C.A. Regulation of PtdIns(3,4,5)P3/Akt signalling by inositol polyphosphate 5-phosphatases. *Biochem. Soc. Trans.* **2016**, *44*, 240–252. [CrossRef]

163. Bielas, S.L.; Silhavy, J.L.; Brancati, F.; Kisseleva, M.V.; Al-Gazali, L.; Sztrohia, L.; Bayoumi, R.A.; Zaki, M.S.; Abdel-Aleem, A.; Rosti, R.O.; et al. Mutations in INPP5E, encoding inositol polyphosphate-5-phosphatase E, link phosphatidylinositol signaling to the ciliopathies. *Nat. Genet.* **2009**, *41*, 1032–1036. [CrossRef] [PubMed]
Cells 2021, 10, 3602

177. Hakim, S.; Dyson, J.M.; Feeney, S.J.; Davies, E.M.; Sriratana, A.; Koenig, M.N.; Plotnikova, O.V.; Smyth, I.M.; Ricardo, S.D.; Hobbs, R.M.; et al. Inpp5e suppresses polycystic kidney disease via inhibition of PI3K/Akt-dependent mTORC1 signaling. *Hum. Mol. Genet.* 2016, 25, 2293–2315. [CrossRef]

178. Xu, W.; Jin, M.; Hu, R.; Wang, H.; Zhang, F.; Yuan, S.; Cao, Y. The Joubert Syndrome Protein Inpp5e Controls Ciliogenesis by Regulating Phosphoinositides at the Apical Membrane. *J. Am. Soc. Nephrol.* 2017, 28, 118–129. [CrossRef]

179. Sierra Potchanant, E.A.; Cerabona, D.; Sater, Z.A.; He, Y.; Sun, Z.; Gehlhausen, J.; Nalepa, G. INPP5E Preserves Genomic Stability through Regulation of Mitosis. *Mol. Cell. Biol.* 2017, 37. [CrossRef] [PubMed]

180. Ivan, M.; Kondo, K.; Yang, H.; Kim, W.; Valiando, J.; Ohh, M.; Salic, A.; Asara, J.M.; Lane, W.S.; Kaelin, W.G. J. HIFalpha targeted for VHL-mediated destruction by proline hydroxylation: Implications for O2 sensing. *Science* 2001, 292, 464–468. [CrossRef]

181. Epstein, A.C.; Gleadle, J.M.; McNell, L.A.; Hewitson, K.S.; O’Rourke, J.; Mole, D.R.; Mukherji, M.; Metzen, E.; Wilson, M.I.; Dhanda, A.; et al. C. elegans EGL-9 and mammalian homologs define a family of dioxygenases that regulate HIF by prolyl hydroxylation. *Cell* 2001, 107, 43–54. [CrossRef]

182. Hon, W.C.; Wilson, M.I.; Harlos, K.; Claridge, T.D.; Schofield, C.J.; Pugh, C.W.; Maxwell, P.H.; Ratcliffe, P.J.; Stuart, D.I.; Jones, E.Y. Structural basis for the recognition of hydroxyproline in HIF-1 alpha by pVHL. *Nature* 2002, 417, 975–978. [CrossRef]

183. Gossage, L.; Eisen, T.; Maher, E.R. VHL, the story of a tumour suppressor gene. *Nat. Rev. Cancer* 2015, 15, 55–64. [CrossRef] [PubMed]

184. Chittiboina, P.; Lonser, R.R. Von Hippel-Lindau disease. *Handb. Clin. Neurol.* 2015, 132, 139–156. [CrossRef] [PubMed]

185. Lutz, M.S.; Burke, R.D. Primary cilium formation requires von hippel-lindau gene function in renal-derived cells. *Cancer Res.* 2006, 66, 6903–6907. [CrossRef]

186. Guo, J.; Chakraborty, A.A.; Liu, P.; Gan, W.; Zheng, X.; Inuzuka, H.; Wang, B.; Zhang, J.; Zhang, L.; Yuan, M.; et al. pVHL suppresses kinase activity of Akt in prolyl-hydroxylation-dependent manner. *Science* 2016, 353, 929–932. [CrossRef] [PubMed]

187. Minervini, G.; Pennuto, M.; Tosatto, S.C.E. The pVHL neglected functions, a tale of hypoxia-dependent and -independent actions. *Cell Chem. Biol.* 2017, 24, 660–671. [CrossRef] [PubMed]

188. Guo, J.; Chakraborty, A.A.; Liu, P.; Gan, W.; Zheng, X.; Inuzuka, H.; Wang, B.; Zhang, J.; Zhang, L.; Yuan, M.; et al. Structural basis for the recognition of hydroxyproline in HIF-1 alpha by pVHL. *Nature* 2002, 417, 975–978. [CrossRef]

189. Nakamura, T.; Fujita, Y.; Sato, M.; Tsukada, T.; Tsukada, Y.; Ito, M.; Sakurai, Y.; Sano, H.; Ikeda, S.; et al. pVHL suppresses kinase activity of Akt in prolyl hydroxylation-dependent manner. *Science* 2001, 292, 464–468. [CrossRef]

190. Epstein, A.C.; Gleadle, J.M.; McNell, L.A.; Hewitson, K.S.; O’Rourke, J.; Mole, D.R.; Mukherji, M.; Metzen, E.; Wilson, M.I.; Dhanda, A.; et al. C. elegans EGL-9 and mammalian homologs define a family of dioxygenases that regulate HIF by prolyl hydroxylation. *Cell* 2001, 107, 43–54. [CrossRef]

191. Hou, W.; Ji, Z. Generation of autochthonous mouse models of clear cell renal cell carcinoma: Mouse models of renal cell carcinoma. *Exp. Mol. Med.* 2018, 50, 1–10. [CrossRef] [PubMed]

192. Guo, H.; German, P.; Bai, S.; Barnes, S.; Guo, W.; Qi, X.; Lou, H.; Liang, J.; Jonasch, E.; Mills, G.B.; et al. The PI3K/AKT Pathway and Renal Cell Carcinoma. *J. Genet. Genom.* 2015, 42, 343–353. [CrossRef] [PubMed]

193. Cohen, P.; Cross, D.; Jänne, P.A. Kinase drug discovery 20 years after imatinib: Progress and future directions. *Nat. Rev. Drug Discov.* 2021, 20, 551–569. [CrossRef] [PubMed]

194. McIntyre, P.J.; Collins, P.M.; Vrzel, L.; Birchall, K.; Arnold, L.H.; Mpamhanga, C.; Coombs, P.J.; Burgess, S.G.; Richards, M.W.; Winter, A.; et al. Characterization of Three Druggable Hot-Spots in the Aurora-A/TPX2 Interaction Using Biochemical, Biophysical, and Fragment-Based Approaches. *ACS Chem. Biol.* 2017, 12, 2906–2914. [CrossRef] [PubMed]

195. Narvaez, G.; Pennuto, M.; Tosatto, S.C.E. The pVHL neglected functions, a tale of hypoxia-dependent and -independent actions. *Cell Chem. Biol.* 2017, 24, 660–671. [CrossRef] [PubMed]

196. Ran, X.; Gestwicki, J.E. Inhibitors of protein–protein interactions (PPIs): An analysis of scaffold choices and buried surface area. *Curr. Opin. Chem. Biol.* 2018, 44, 75–86. [CrossRef]

197. Kufer, T.A.; Silljé, H.H.; Körner, R.; Gruss, O.J.; Meraldi, P.; Nigg, E.A. Human TPX2 is required for targeting Aurora-A kinase to the spindle. *J. Cell Biol.* 2002, 158, 617–623. [CrossRef]

198. Bird, A.W.; Hyman, A.A. Building a spindle of the correct length in human cells requires the interaction between TPX2 and Aurora A. *J. Cell Biol.* 2008, 182, 289–300. [CrossRef]

199. Gupta, P.; Mohanty, D. SMMPPI: A machine learning-based approach for prediction of modulators of protein-protein interactions and its application for identification of novel inhibitors for RBD-hACE2 interactions in SARS-CoV-2. *Brief. Bioinform.* 2021, 22. [CrossRef] [PubMed]

200. Choi, J.; Yun, J.S.; Song, H.; Kim, N.H.; Kim, H.S.; Yook, J.I. Exploring the chemical space of protein–protein interaction inhibitors through machine learning. *Sci. Rep.* 2021, 11, 13369. [CrossRef]

201. Lu, H.; Zhou, Q.; He, J.; Jiang, Z.; Peng, C.; Tong, R.; Shi, J. Recent advances in the development of protein–protein interactions modulators: Mechanisms and clinical trials. *Signal Transduct. Target. Ther.* 2020, 5, 213. [CrossRef]

202. Lai, A.C.; Creews, C.M. Induced protein degradation: An emerging drug discovery paradigm. *Nat. Rev. Drug Discov.* 2017, 16, 101–114. [CrossRef]
203. Naito, M.; Ohoka, N.; Shibata, N. SNIPERs-Hijacking IAP activity to induce protein degradation. Drug Discov. Today Technol. 2019, 31, 35–42. [CrossRef]

204. He, M.; Lv, W.; Rao, Y. Opportunities and Challenges of Small Molecule Induced Targeted Protein Degradation. Front. Cell Dev. Biol. 2021, 9. [CrossRef] [PubMed]

205. Agnew, H.D.; Coppock, M.B.; Idso, M.N.; Lai, B.T.; Liang, J.; McCarthy-Torrens, A.M.; Warren, C.M.; Heath, J.R. Protein-Catalyzed Capture Agents. Chem. Rev. 2019, 119, 9950–9970. [CrossRef]

206. Wang, Y.; Jiang, X.; Feng, F.; Liu, W.; Sun, H. Degradation of proteins by PROTACs and other strategies. Acta Pharm. Sin. B 2020, 10, 207–238. [CrossRef]

207. Sells, T.B.; Chau, R.; Ecsedy, J.A.; Gershman, R.E.; Hoar, K.; Huck, J.; Janowick, D.A.; Kadambi, V.J.; LeRoy, P.J.; Stirling, M.; et al. MLN8054 and Alisertib (MLN8237): Discovery of Selective Oral Aurora A Inhibitors. ACS Med. Chem. Lett. 2015, 6, 630–634. [CrossRef] [PubMed]

208. You, I.; Erickson, E.C.; Donovan, K.A.; Eleuteri, N.A.; Fischer, E.S.; Gray, N.S.; Toker, A. Discovery of an AKT Degrader with Prolonged Inhibition of Downstream Signaling. Cell Chem. Biol. 2020, 27, 66–73.e67. [CrossRef] [PubMed]

209. Henning, R.K.; Varghese, J.O.; Das, S.; Nag, A.; Tang, G.; Tang, K.; Sutherland, A.M.; Heath, J.R. Degradation of Akt using protein-catalyzed capture agents. J. Pept. Sci. 2016, 22, 196–200. [CrossRef] [PubMed]

210. Brès, V.; Yoh, S.M.; Jones, K.A. The multi-tasking P-TEFb complex. Curr. Opin. Cell Biol. 2008, 20, 334–340. [CrossRef] [PubMed]

211. Bechter, O.; Schöffski, P. Make your best BET: The emerging role of BET inhibitor treatment in malignant tumors. Pharmacol. Ther. 2020, 208, 107479. [CrossRef]

212. Lim, S.L.; Xu, L.; Han, B.C.; Shyamsunder, P.; Chng, W.J.; Koeffler, H.P. Multiple myeloma: Combination therapy of BET proteolysis targeting chimeric molecule with CDK9 inhibitor. PloS ONE 2020, 15, e0232068. [CrossRef] [PubMed]

213. Qi, S.-M.; Dong, J.; Xu, Z.-Y.; Cheng, X.-D.; Zhang, W.-D.; Qin, J.-J. PROTAC: An Effective Targeted Protein Degradation Strategy for Cancer Therapy. Front. Pharmacol. 2021, 12. [CrossRef]

214. Bertolin, G.; Sizaire, F.; Herbomel, G.; Reboutier, D.; Prigent, C.; Tramier, M. A FRET biosensor reveals spatiotemporal activation and functions of aurora kinase A in living cells. Nat. Commun. 2016, 7, 12674. [CrossRef] [PubMed]

215. Miura, H.; Matsuda, M.; Aoki, K. Development of a FRET Biosensor with High Specificity for Akt. Cell Struct. Funct. 2014, 39, 9–20. [CrossRef] [PubMed]

216. Agarwal, S.R.; Gratwohl, J.; Cozad, M.; Yang, P.C.; Clancy, C.E.; Harvey, R.D. Compartmentalized cAMP Signaling Associated With Lipid Raft and Non-raft Membrane Domains in Adult Ventricular Myocytes. Front. Pharmacol. 2018, 9, 332. [CrossRef]

217. Jiang, J.Y.; Falcone, J.L.; Curci, S.; Hofer, A.M. Direct visualization of cAMP signaling in primary cilia reveals up-regulation of ciliary GPCR activity following Hedgehog activation. Proc. Natl. Acad. Sci. USA 2019, 116, 12066–12071. [CrossRef] [PubMed]

218. Lee, K.L.; Guevarra, M.D.; Nguyen, A.M.; Chua, M.C.; Wang, Y.; Jacobs, C.R. The primary cilium functions as a mechanical and calcium signaling nexus. Cilia 2015, 4, 7. [CrossRef] [PubMed]

219. Ni, Q.; Titov, D.V.; Zhang, J. Analyzing protein kinase dynamics in living cells with FRET reporters. Methods 2006, 40, 279–286. [CrossRef]

220. Mukherjee, S.; Jansen, V.; Jikeli, J.F.; Hamzeh, H.; Alvarez, L.; Dombrowski, M.; Balbach, M.; Strünker, T.; Seifert, R.; Kaupp, U.B.; et al. A novel biosensor to study cAMP dynamics in cilia and flagella. eLife 2016, 5, e14052. [CrossRef]

221. Arslanhan, M.D.; Gulesoy, D.; Firat-Karalar, E.N. A Proximity Mapping Journey into the Biology of the Mammalian Centrosome/Cilium Complex. Cells 2020, 9, 1390. [CrossRef] [PubMed]

222. Devi, R.; Pelletier, L.; Prosster, S.L. Charting the complex composite nature of centrosomes, primary cilia and centriolar satellites. Curr. Opin. Struct. Biol. 2021, 66, 32–40. [CrossRef] [PubMed]

223. Kim, S.; Carruthers, N.; Lee, J.; Chinni, S.; Stemmer, P. Classification-based quantitative analysis of stable isotope labeling by amino acids in cell culture (SILAC) data. Comput. Methods Programs Biomed. 2016, 137, 137–148. [CrossRef]

224. Duggal, S.; Jallkiani, N.; Midha, M.K.; Agrawal, N.; Rao, K.V.S.; Kumar, A. Defining the Akt1 interactome and its role in regulating the cell cycle. Sci. Rep. 2018, 8, 1303. [CrossRef]