

JB Review

Post-translational modification enzymes as key regulators of ciliary protein trafficking

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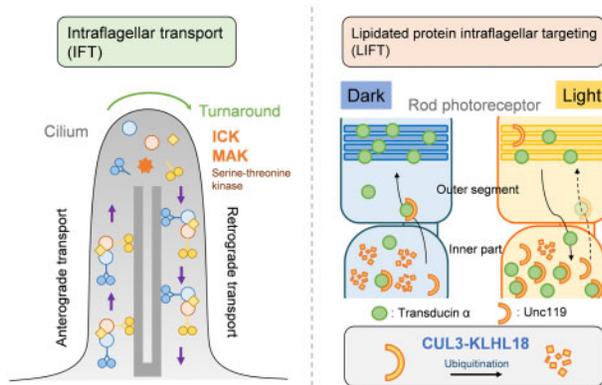
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Primary cilia are evolutionarily conserved microtubule-based organelles that protrude from the surface of almost all cell types and decode a variety of extracellular stimuli. Ciliary dysfunction causes human diseases named ciliopathies, which span a wide range of symptoms, such as developmental and sensory abnormalities. The assembly, disassembly, maintenance and function of cilia rely on protein transport systems including intraflagellar transport (IFT) and lipidated protein intraflagellar targeting (LIFT). IFT is coordinated by three multisubunit protein complexes with molecular motors along the ciliary axoneme, while LIFT is mediated by specific chaperones that directly recognize lipid chains. Recently, it has become clear that several post-translational modification enzymes play crucial roles in the regulation of IFT and LIFT. Here, we review our current understanding of the roles of these post-translational modification enzymes in the regulation of ciliary protein trafficking as well as their regulatory mechanisms, physiological significance and involvement in human diseases.

Graphical Abstract



Keywords: ICK/CILK1; kinase; MAK; retina; ubiquitin.

Abbreviations: BBS, Bardet-Biedl syndrome; CK2, casein kinase 2; FGF, fibroblast growth factor; IFT, intraflagellar transport; LIFT, lipidated protein intraflagellar targeting.

The primary cilium is a hair-like microtubule-based structure that protrudes from the surface of nearly every cell and performs a wide range of sensory functions across species (1, 2). The ciliary membrane and interior are distinguished from the plasma membrane and the cytoplasm, respectively, by the presence of the transition zone and the transition fibres (3). A variety of signalling receptors localize to primary cilia and receive extracellular stimuli including light, odorants and Hedgehog morphogens. For example, retinal photoreceptor cells develop the outer segment, a light-sensory structure containing components of the phototransduction cascade including photopigments, which are formed initially from the primary cilia in photoreceptor precursors (4). Therefore, cilia function as a signalling centre for multiple transduction pathways. Ciliary dysfunction leads to human diseases termed ‘ciliopathies’, which are characterized by a broad spectrum of symptoms, including polydactyly, cranio-facial abnormalities, brain malformation, obesity, polycystic kidney, anosmia, hearing loss and retinal degeneration (5–7).

Intraflagellar Transport

The biogenesis and maintenance of cilia depend on intraflagellar transport (IFT), the bidirectional protein trafficking system coordinated by three large protein complexes, IFT-B, IFT-A and the BBSome, with molecular motors along the axonemal microtubules of cilia. They assemble into linear arrays, known as IFT trains, which mediate ciliary protein transport along the axoneme in both anterograde and retrograde directions (8). In addition, the three IFT complexes function in ciliary import and export of proteins (9, 10). IFT-B, a 16-subunit complex, mediates anterograde transport from the base to the tip driven by the kinesin-2 motor, whereas IFT-A, a 6-subunit complex, mediates retrograde transport from the tip back to the base driven by the cytoplasmic dynein-2 motor (9, 11). The BBSome, an 8-subunit complex, functions as a coat adaptor for IFT-B and mediates the exit of membrane proteins including GPCRs from cilia (9, 12, 13). In addition, it also assists the assembly of IFT trains at the ciliary base (14). At the ciliary tip, IFT trains are disassembled and then reassembled for turnaround and retrograde transport (15). Mutations in some genes encoding components of IFT trains are known to be associated with ciliopathies including Bardet-Biedl syndrome (BBS) and Joubert syndrome (16).

Serine–Threonine Kinases MAK and ICK in the Regulation of Ciliary Protein Trafficking

Various serine–threonine kinases play crucial roles in many aspects of cilia assembly, disassembly, maintenance and function. Two serine–threonine kinases from

a branch of CDK/MAPK/GSK3/CLK (CMGC) kinases, male germ cell-associated kinase (MAK) and intestinal cell kinase (ICK), also known as ciliogenesis-associated kinase 1 (CILK1), are proposed to serve as regulators of IFT turnaround at the ciliary tip and ciliary length in mammalian cells (Fig. 1). Since IFT

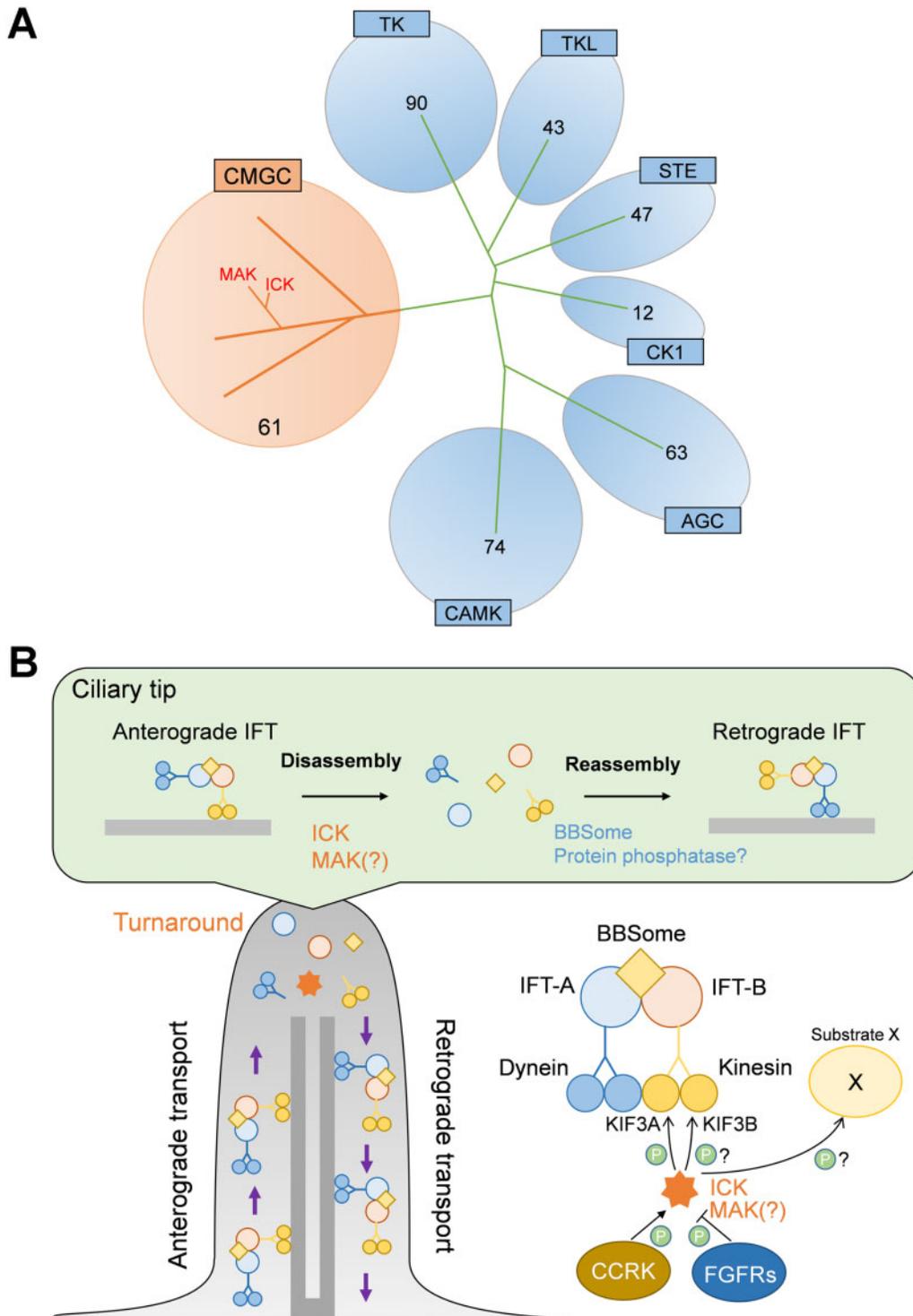


Fig. 1. The serine–threonine kinases MAK and ICK in the regulation of IFT. (A) Phylogenetic distribution of protein kinases in humans. MAK and ICK are classified into the CMGC kinase family. TK, Tyrosine kinase; TKL, Tyrosine kinase-like; STE, Homologs of yeast Sterile 7, Sterile 11, Sterile 20 kinases; CK1, Casein kinase 1; AGC, Containing PKA, PKG, PKC families; CAMK, Calcium/calmodulin-dependent protein kinase; CMGC, Containing CDK, MAPK, GSK3, CLK families. Numbers of kinases classified into each family are indicated (110). (B) Proposed model of the regulation of IFT turnaround at the ciliary tip by MAK and ICK.

plays a key role in ciliary length control, regulation of IFT is thought to be important for the ciliary length regulation (17). As the names imply, *Mak* and *Ick* were originally identified in male germ cells and intestinal crypt cells, respectively (18, 19). MAK and ICK are evolutionarily conserved mitogen-activating protein kinase-like kinases that exhibit high homology, especially in their catalytic domains (19–21). *Mak* is predominantly expressed in the retina and testis whereas *Ick* is ubiquitously expressed among tissues (22). In contrast to the distinct tissue distribution patterns, these protein kinases show a similar subcellular localization. MAK localizes to the distal region of ciliary axonemes in retinal photoreceptor cells (23). ICK localizes mainly to the ciliary tip, which is mediated through the anterograde trafficking by IFT-B (24, 25). *Caenorhabditis elegans* DYF-5, an orthologue of MAK and ICK, is an IFT cargo molecule transported to the distal segments of sensory cilia (26). In addition, ICK is enriched in ciliary vesicles released from the tip of cilia (27). *Mak*-deficient mice exhibit elongated photoreceptor ciliary axonemes with the accumulation of IFT88, an IFT-B component, at the distal portion (23). Loss-of-function of ICK causes shortened or elongated cilia, impaired Hedgehog signaling and accumulation of IFT-B, IFT-A and BBSome components at ciliary tips, while ICK overexpression induces accumulation of IFT-B, but not IFT-A and BBSome components at the tip of cilia, suggesting roles of ICK in disassembly of IFT trains in the turnaround process (24, 25, 28–32). *Chlamydomonas reinhardtii* (*Chlamydomonas*) LF4, *Tetrahymena* LF4A, *Leishmania mexicana* LmxMPK9, and *C. elegans* DYF-5, orthologues of MAK and ICK, are also involved in the regulation of IFT as well as cilia/flagella length and formation (26, 33–37).

ICK phosphorylates the C-terminal portion of KIF3A, a subunit of kinesin-2, including Thr674 (24, 38). KIF3A Thr674 is positioned in a consensus amino acid sequence for MAK and ICK phosphorylation that is evolutionarily conserved (39). Localization of KIF3A phosphorylated at Thr674 to ciliary tips is observed in mouse embryonic fibroblasts, which is attenuated by *Ick* deficiency. Inhibition of phosphorylation on serine/threonine residues including Thr674 at the KIF3A C-terminal portion perturbs cilia formation in cultured cells and zebrafish (24). Mouse embryonic fibroblasts carrying a Thr-to-Ala mutation at residue 674 on KIF3A (KIF3A T674A) show slightly elongated cilia without affecting ciliary localization of IFT88 (40). These observations suggest that ICK phosphorylates other substrate protein(s) in addition to the KIF3A C-terminal portion including Thr674 to regulate IFT and ciliary length. In *Chlamydomonas*, phosphorylation of the kinesin-2 motor subunit FLA8, an orthologue of KIF3B, at Ser663 is required for IFT turnaround at the flagellar tip (41). Intriguingly, FLA8 Ser663 is located in a consensus amino acid sequence for phosphorylation by MAK and ICK that is evolutionarily conserved among species, suggesting that IFT turnaround at the ciliary tip is mediated by phosphorylation of KIF3B in addition to KIF3A by MAK and

ICK in mammals. *C. elegans* hypomorphic mutants of *bbs-1*, a gene encoding a BBSome component, show accumulation of IFT-B but not IFT-A components at the ciliary tip, as similarly observed in ICK overexpressing cells (14). Given that the BBSome assembles IFT trains at the ciliary base, disassembly and reassembly of IFT trains at the ciliary tip may be mediated by ICK, as well as probably MAK, and the BBSome, respectively.

MAK and ICK in Development, Physiology and Disease

Mak-deficient mice are viable and fertile without obvious developmental abnormalities, but exhibit progressive retinal photoreceptor degeneration (23). Interestingly, mutations in human *MAK* gene were discovered in patients with autosomal recessive retinitis pigmentosa (RP), a retinal degenerative disease (42, 43). In contrast, *Ick*-deficient mice exhibit neonatal lethality accompanied with developmental abnormalities observed in multiple organ systems including the bone, lung, kidney, brain, retina, and inner ear (44). In humans, two homozygous loss-of-function mutations in *ICK* gene, R272Q and G120C, are associated with endocrine-cerebro-osteodysplasia (ECO) syndrome, an autosomal recessive ciliopathy characterized by neonatal lethality with multiple defects involving the endocrine, cerebral, and skeletal systems (31, 45). Another homozygous loss-of-function mutation in human *ICK* gene, E80K, is associated with short rib-polydactyly syndrome (SRPS), an autosomal recessive ciliopathy showing perinatal lethality with short ribs, shortened and hypoplastic long bones, polydactyly and multiorgan system abnormalities (30). In addition, heterozygous variants in human *ICK* gene are linked to juvenile myoclonic epilepsy (46). Of them, four strongly linked variants, K220E, K305T, A615T and R632X, affect ICK functions in cilia formation and impair mitosis, cell-cycle exit and radial neuroblast migration while promoting apoptosis in the cerebral cortex (46, 47). In contrast to *Ick*-deficient mice, homozygous KIF3A T674A knock-in mice exhibit mildly reduced alveolar airspace in the lung, but are viable without gross abnormalities in the bone and brain, suggesting that other substrate(s) in addition to KIF3A Thr674 are phosphorylated by ICK *in vivo*.

Regulatory Mechanisms of MAK and ICK Activities

MAK and ICK are activated by phosphorylation at the TDY motif in their kinase domain by cell cycle-related kinase (CCRK) *in vitro* (39). ICK phosphorylation by CCRK negatively regulates ciliogenesis in cultured cells (48). Similar to loss of *Mak* or *Ick*, *Ccrk* deficiency causes dysregulation of cilia length and accumulation of IFT88 at ciliary tips (49). *Ccrk*-deficient mice show multiple developmental abnormalities associated with dysregulation of Hedgehog signaling, including polydactyly, neural tube patterning defects and malformation of the lung and eye (49–51). CCRK orthologues, *Chlamydomonas* LF2 and *C. elegans*

DYF-18, also participates in the IFT regulation as well as cilia/flagella length and formation control (26, 36, 52, 53). LF4 phosphorylation at the TDY motif is diminished in the *Chlamydomonas lf-2* mutant, suggesting that the LF2-LF4 signaling axis is evolutionarily conserved among species (54). In contrast to CCRK, fibroblast growth factor (FGF) signalling is thought to negatively regulate the ICK activity. Inactivation of Fgf receptor 1 (Fgfr1) or its ligands results in shortened cilia in zebrafish and *Xenopus* (55). On the other hand, FGFR3 activation shortened cilia and perturbed the localization of IFT20, an IFT-B component, to cilia in mammals (56, 57). Biochemical experiments show that FGFRs interact with, phosphorylate and inactivate ICK. In cultured cells, FGF treatment modulates cilia length through ICK (58).

Lipidated Protein Intraflagellar Targeting in Retinal Photoreceptor Cells

In parallel to IFT, lipidated protein intraflagellar targeting (LIFT) plays crucial roles in establishing a dynamic ciliary signaling compartment (59). Transport of some lipidated proteins into cilia relies on specific chaperones uncoordinated 119 (UNC119) and phosphodiesterase 6 δ (PDE6 δ), which directly recognize lipid chains in the cytoplasmic region and unload their cargoes inside cilia upon interacting with the small ARF-like GTPase protein ARL3 bound to GTP (60–63). ARL3 is converted from its inactive GDP-bound state to the active GTP-bound state inside cilia by ARL13B, a guanine nucleotide exchange factor (GEF) constitutively localized to cilia (64). In contrast, retinitis pigmentosa 2 (RP2), a GTPase-activating protein (GAP) localized at the base of cilia, is predicted to keep ARL3 in its GDP-bound state outside cilia (65, 66).

Molecular mechanisms and physiological roles of LIFT have been well studied in retinal rod and cone photoreceptor cells. Rod photoreceptor cells are sensitive to light and are responsible for low light vision, while cone photoreceptor cells operate at a brighter range of light intensities and are responsible for high-resolution daylight and colour vision. Subcellular localization of rod transducin, a heterotrimeric G protein that is a mediator of the phototransduction cascade, changes responding to ambient light (67–71). The inner part and outer segment of the photoreceptor cell are connected by a connecting cilium. Rod transducin is transported to the outer segment from the inner part through the connecting cilium, and then concentrated in the outer segment under dark-adapted conditions. After light reception, rod transducin translocates from the outer segment to the inner part through the connecting cilium. This light- and dark-dependent translocation of transducin modulates photosensitivity in rod photoreceptors, thereby contributing to light and dark adaptation. Localization of the α -subunit of rod transducin (rT α) to the outer segment is required for normal light sensitivity of rod photoreceptors (72). In contrast, light-dependent rT α translocation from the outer segment to the inner part protects the retina from the light-induced damage

(73–76). UNC119 interacts with the acylated N-termini of rT α and suppresses rhodopsin-mediated transducin activation (63, 77). The dark-triggered transport of rT α to the outer segment is inhibited in the *Unc119*-deficient mouse retina (63). Deletion of *unc-119* in *C. elegans* also blocks G protein trafficking to cilia, suggesting an evolutionarily conserved role of UNC119 (63). *Unc119*-deficient mice exhibit a slowly progressive retinal degeneration (78). A heterozygous stop codon (K57X) was found in the human *UNC119* gene of an individual with late-onset dominant cone dystrophy (79). Transgenic mice carrying the identical mutation show mitochondrial ANT-1-mediated retinal degeneration (79, 80). On the other hand, PDE6 δ , encoded by *Pde6d*, is a prenyl-binding protein that promotes translocation of the $\beta\gamma$ -subunit of rod transducin (rT $\beta\gamma$) from the inner part to the outer segment. In the *Pde6d*^{-/-} mouse retina, rT γ , known to be farnesylated, mislocalizes to the inner part (81, 82). In addition to rT γ , several components of the phototransduction cascade are also prenylated in rod and cone photoreceptors. PDE6 α and PDE6 β , rod cGMP phosphodiesterase catalytic subunits, PDE6 α' , a cone cGMP phosphodiesterase catalytic subunit and rhodopsin kinase (GRK1) are farnesylated or geranylgeranylated (83–85). Reduced localization of GRK1 and PDE6 α' to the outer segment as well as mislocalization of rod PDE6 subunits to the inner part are observed in *Pde6d*^{-/-} rod and cone photoreceptors (82). As a consequence, loss of *Pde6d* results in altered electrophysiological properties of photoreceptor cells and a slowly progressing retinal degeneration (82). Consistent with *Unc119* and *Pde6d* deficiency, *Arl3* conditional knockout mice show trafficking defects of lipidated proteins including rT α , rT γ , rod PDE6 and GRK1 to outer segments in rod photoreceptors and subsequent retinal degeneration (86). A mutation in the human *ARL3* gene is linked to autosomal dominant RP (87). Deletion of *Arl13b* in the mouse retina leads to mislocalization of rT α and rod PDE6 subunits but faster retinal degeneration than *Arl3* deficiency does, suggesting additional functions of ARL13B other than a GEF for ARL3 in rod photoreceptor cells (88, 89). In humans, mutations in the *ARL13B* gene are associated with Joubert syndrome, an autosomal recessive ciliopathy characterized by multiple symptoms including retinal degeneration (90, 91). *Rp2*-deficient mice exhibit defects in trafficking of GRK1 as well as rod and cone PDE6 to the outer segment, and subsequent slowly progressing retinal degeneration (92). Mutations in the human *RP2* gene are associated with X-linked RP, macular atrophy and cone-rod dystrophy (93–95).

Regulation of Transducin Translocation During Light-Dark Adaptation by the CUL3-KLHL18 Ubiquitin Ligase

The ubiquitin proteasome system is one of the fundamental regulatory tools used by eukaryotic cells. Cullin-RING (really interesting new gene) ubiquitin ligases (CRLs) form one of the largest groups of ubiquitin E3 ligases that regulate diverse cellular pathways (96). Cullin-3 (CUL3) bridges the interaction

between the RING protein RBX1 and substrate adaptors which deliver targets for ubiquitination and proteasomal degradation (97). Covalent attachment of the ubiquitin-like protein NEDD8 to Cullin family proteins is required for the activation of the Cullin-based ubiquitin E3 ligases (98). The N-terminus of CUL3 interacts with the Broad Complex, Tramtrack, Bric-a-Brac (BTB) domain of substrate adaptors including the Kelch-like (KLHL) family proteins, which contain one BTB domain, one BTB and C-terminal kelch (BACK) domain, and five to six Kelch repeats (Fig. 2A) (99). The HUGO Gene Nomenclature Committee (HGNC) presently defines 42 KLHL genes.

Recently, *Kelch-like 18 (Klhl18)*, one of the *Klhl* genes, was found to be predominantly expressed in retinal photoreceptor cells. *Klhl18*-deficient mice exhibit decreased light responses in rod photoreceptors and rTx mislocalization from the outer segment to the inner part. Loss of *Klhl18* or treatment of MLN4924, a small molecule inhibitor of the NEDD8-activating enzyme (NAE) (100), suppresses light-induced retinal degeneration. The CUL3-KLHL18 ubiquitin ligase ubiquitinates and degrades UNC119 in rod photoreceptor cells, preferentially under dark conditions. UNC119 overexpression phenocopies the rTx mislocalization observed in the *Klhl18*^{-/-} mouse retina. These observations suggest that CUL3-KLHL18

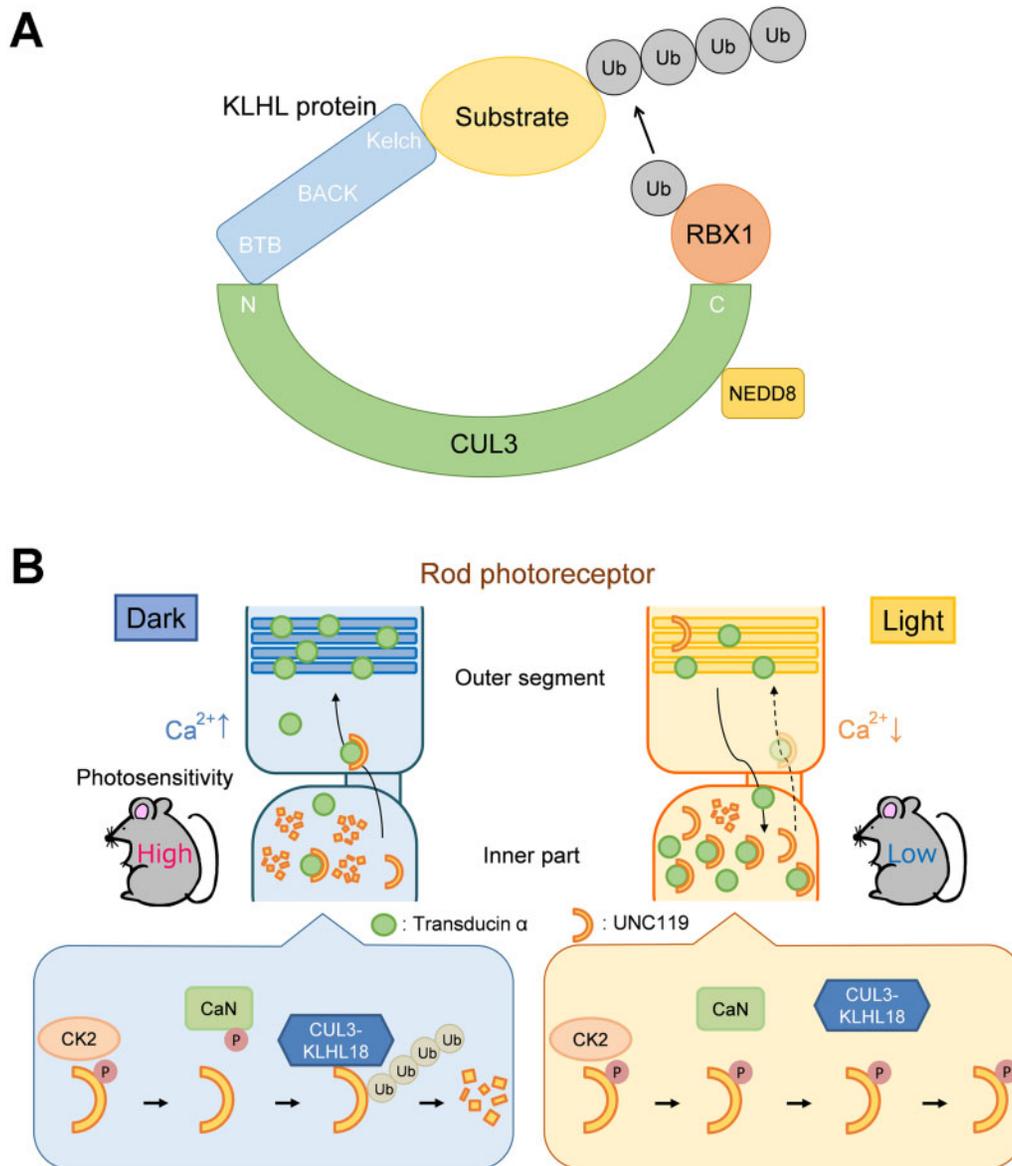


Fig. 2. The CUL3-KLHL18 ubiquitin ligase in the regulation of LIFT. (A) Schematic diagram of CUL3-KLHL ubiquitin ligases. (B) Proposed model of the α -subunit of rod transducin (rTx) translocation during light and dark adaptation in rod photoreceptor cells. In rod photoreceptors, intracellular Ca^{2+} concentration under dark conditions is higher than that under light conditions. In darkness, CK2-phosphorylated UNC119 is dephosphorylated by calcineurin, a Ca^{2+} -dependent phosphatase. CUL3-KLHL18 efficiently ubiquitinates and degrades the dephosphorylated UNC119, thereby facilitating rTx transport from the inner part to the outer segment. In the light, calcineurin-mediated dephosphorylation of CK2-phosphorylated UNC119 is suppressed due to low Ca^{2+} concentration. Inefficient ubiquitination and degradation of the phosphorylated UNC119 by CUL3-KLHL18 results in increased amounts of UNC119 and subsequent inhibition of rTx translocation to the outer segment. CaN, calcineurin.

modulates rT α translocation during light and dark adaptation through UNC119 ubiquitination and degradation. Furthermore, regulatory mechanisms underlying the CUL3-KLHL18-UNC119 axis were investigated. The phosphorylation level of UNC119 is elevated under light conditions compared with that under dark conditions. UNC119 is phosphorylated by casein kinase 2 (CK2), which is a serine/threonine kinase expressed in retinal photoreceptor cells (101). In contrast, UNC119 is dephosphorylated by Calcineurin, a Ca²⁺- and calmodulin-dependent serine/threonine protein phosphatase (102, 103). UNC119 degradation by CUL3-KLHL18 is suppressed and facilitated by UNC119 phosphorylation and dephosphorylation, respectively. Inhibition of CK2 decreases the amount of UNC119 in the retina, while inhibition of Calcineurin increases the retinal expression level of UNC119, causes rT α mislocalization to the inner part of photoreceptors, and protects the retina from light-induced damage. Collectively, these results suggest that CUL3-KLHL18 promotes UNC119 ubiquitination and degradation depending on phosphorylation, thereby regulating light- and dark-dependent rT α translocation in the retina (Fig. 2B) (104). Given that light exposure is a suspected risk factor for the progression of age-related macular degeneration and RP (105–108), inhibition of this signaling pathway may be a potential therapeutic target.

Concluding Remarks

It has recently become clear that several post-translational modification enzymes play key roles in the regulation of ciliary protein trafficking. Cumulative evidence of the functional mechanisms of MAK and ICK has unravelled many aspects of the physiological significance of the coordinated IFT turnaround at the ciliary tip and its involvement in human ciliopathies. Identification and functional characterization of the CUL3-KLHL18 ubiquitin ligase in retinal photoreceptor cells put forward our knowledge of a series of regulatory mechanisms from photoreception to light-dark adaptation. However, these findings raise new questions. For example, assuming that IFT trains are disassembled by MAK and ICK at the ciliary tip, how are they reassembled for retrograde IFT? In parallel to the BBSome as mentioned above, serine-threonine phosphatase(s) may also contribute to re-assembly of IFT trains at the ciliary tip through dephosphorylating KIF3A and other substrate(s). In addition, although rT $\beta\gamma$ also shows light- and dark-dependent translocation between the outer segment and the inner part of retinal photoreceptor cells, which modulates rod light responses (109), rT $\beta\gamma$ translocation is independent of CUL3-KLHL18. PDE6 δ ubiquitination and degradation by an unknown E3 ubiquitin ligase may underpin rT $\beta\gamma$ translocation during light and dark adaptation. Further analyses are needed to unveil comprehensive regulatory mechanisms underlying ciliary protein trafficking, whose understanding would contribute to develop therapeutic strategies to treat human diseases.

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Conflict of interest

None declared.

References

- Gerdes, J.M., Davis, E.E., and Katsanis, N. (2009) The vertebrate primary cilium in development, homeostasis, and disease. *Cell* **137**, 32–45
- Malicki, J.J., and Johnson, C.A. (2017) The cilium: cellular antenna and central processing unit. *Trends Cell Biol.* **27**, 126–140
- Garcia-Gonzalo, F.R., and Reiter, J.F. (2017) Open sesame: how transition fibers and the transition zone control ciliary composition. *Cold Spring Harb. Perspect. Biol.* **9**, a028134.
- Tokuyasu, K., and Yamada, E. (1959) The fine structure of the retina studied with the electron microscope. IV. Morphogenesis of outer segments of retinal rods. *J. Biophys. Biochem. Cytol.* **6**, 225–230
- Fliegeauf, M., Benzing, T., and Omran, H. (2007) When cilia go bad: cilia defects and ciliopathies. *Nat. Rev. Mol. Cell Biol.* **8**, 880–893
- Nigg, E.A., and Raff, J.W. (2009) Centrioles, centrosomes, and cilia in health and disease. *Cell* **139**, 663–678
- Anvarian, Z., Mykytyn, K., Mukhopadhyay, S., Pedersen, L.B., and Christensen, S.T. (2019) Cellular signalling by primary cilia in development, organ function and disease. *Nat. Rev. Nephrol.* **15**, 199–219
- Lechtreck, K.F. (2015) IFT-cargo interactions and protein transport in cilia. *Trends Biochem. Sci.* **40**, 765–778
- Nachury, M.V. (2018) The molecular machines that traffic signaling receptors into and out of cilia. *Curr. Opin. Cell Biol.* **51**, 124–131
- Nakayama, K., and Katoh, Y. (2018) Ciliary protein trafficking mediated by IFT and BBSome complexes with the aid of kinesin-2 and dynein-2 motors. *J. Biochem.* **163**, 155–164
- Rosenbaum, J.L., and Witman, G.B. (2002) Intraflagellar transport. *Nat. Rev. Mol. Cell Biol.* **3**, 813–825
- Wingfield, J.L., Lechtreck, K.F., and Lorentzen, E. (2018) Trafficking of ciliary membrane proteins by the intraflagellar transport/BBSome machinery. *Essays Biochem.* **62**, 753–763
- Ye, F., Nager, A.R., and Nachury, M.V. (2018) BBSome trains remove activated GPCRs from cilia by enabling passage through the transition zone. *J. Cell Biol.* **217**, 1847–1868
- Wei, Q., Zhang, Y., Li, Y., Zhang, Q., Ling, K., and Hu, J. (2012) The BBSome controls IFT assembly and turnaround in cilia. *Nat. Cell Biol.* **14**, 950–957
- Chien, A., Shih, S.M., Bower, R., Tritschler, D., Porter, M.E., and Yildiz, A. (2017) Dynamics of the IFT machinery at the ciliary tip. *Elife* **6**, e28606
- Reiter, J.F., and Leroux, M.R. (2017) Genes and molecular pathways underpinning ciliopathies. *Nat. Rev. Mol. Cell Biol.* **18**, 533–547
- Ishikawa, H., and Marshall, W.F. (2011) Ciliogenesis: building the cell's antenna. *Nat. Rev. Mol. Cell Biol.* **12**, 222–234

18. Matsushime, H., Jinno, A., Takagi, N., and Shibuya, M. (1990) A novel mammalian protein kinase gene (mak) is highly expressed in testicular germ cells at and after meiosis. *Mol. Cell. Biol.* **10**, 2261–2268
19. Togawa, K., Yan, Y.X., Inomoto, T., Slaugenhaupt, S., and Rustgi, A.K. (2000) Intestinal cell kinase (ICK) localizes to the crypt region and requires a dual phosphorylation site found in map kinases. *J. Cell. Physiol.* **183**, 129–139
20. Miyata, Y., and Nishida, E. (1999) Distantly related cousins of MAP kinase: biochemical properties and possible physiological functions. *Biochem. Biophys. Res. Commun.* **266**, 291–295
21. Shinkai, Y., Satoh, H., Takeda, N., Fukuda, M., Chiba, E., Kato, T., Kuramochi, T., and Araki, Y. (2002) A testicular germ cell-associated serine-threonine kinase, MAK, is dispensable for sperm formation. *Mol. Cell. Biol.* **22**, 3276–3280
22. Tsutsumi, R., Chaya, T., and Furukawa, T. (2018) Enriched expression of the ciliopathy gene *Ick* in cell proliferating regions of adult mice. *Gene Expr. Patterns.* **29**, 18–23
23. Omori, Y., Chaya, T., Katoh, K., Kajimura, N., Sato, S., Muraoka, K., Ueno, S., Koyasu, T., Kondo, M., and Furukawa, T. (2010) Negative regulation of ciliary length by ciliary male germ cell-associated kinase (Mak) is required for retinal photoreceptor survival. *Proc. Natl. Acad. Sci. USA.* **107**, 22671–22676
24. Chaya, T., Omori, Y., Kuwahara, R., and Furukawa, T. (2014) ICK is essential for cell type-specific ciliogenesis and the regulation of ciliary transport. *Embo J.* **33**, 1227–1242
25. Nakamura, K., Noguchi, T., Takahara, M., Omori, Y., Furukawa, T., Katoh, Y., and Nakayama, K. (2020) Anterograde trafficking of ciliary MAP kinase-like ICK/CILK1 by the intraflagellar transport machinery is required for intraciliary retrograde protein trafficking. *J. Biol. Chem.* **295**, 13363–13376
26. Yi, P., Xie, C., and Ou, G. (2018) The kinases male germ cell-associated kinase and cell cycle-related kinase regulate kinesin-2 motility in *Caenorhabditis elegans* neuronal cilia. *Traffic* **19**, 522–535
27. Phua, S.C., Chiba, S., Suzuki, M., Su, E., Roberson, E.C., Pusapati, G.V., Schurmans, S., Setou, M., Rohatgi, R., Reiter, J.F., Ikegami, K., and Inoue, T. (2017) Dynamic remodeling of membrane composition drives cell cycle through primary cilia excision. *Cell* **168**, 264–279 e215
28. Moon, H., Song, J., Shin, J.O., Lee, H., Kim, H.K., Eggenschwiller, J.T., Bok, J., and Ko, H.W. (2014) Intestinal cell kinase, a protein associated with endocrine-cerebro-osteodysplasia syndrome, is a key regulator of cilia length and Hedgehog signaling. *Proc. Natl. Acad. Sci. USA.* **111**, 8541–8546
29. Broekhuis, J.R., Verhey, K.J., and Jansen, G. (2014) Regulation of cilium length and intraflagellar transport by the RCK-kinases ICK and MOK in renal epithelial cells. *PLoS One* **9**, e108470
30. Paige Taylor, S., Kunova Bosakova, M., Varecha, M., Balek, L., Barta, T., Trantirek, L., Jelinkova, I., Duran, I., Vesela, I., Forlenza, K.N., Martin, J.H., Hampl, A., University of Washington Center for Mendelian Genomics, Bamshad, M., Nickerson, D., Jaworski, M.L., Song, J., Ko, H.W., Cohn, D.H., Krakow, D., and Krejci, P. (2016) An inactivating mutation in intestinal cell kinase, ICK, impairs hedgehog signalling and causes short rib-polydactyly syndrome. *Hum. Mol. Genet.* **25**, 3998–4011
31. Oud, M.M., Bonnard, C., Mans, D.A., Altunoglu, U., Tohari, S., Ng, A.Y.J., Eskin, A., Lee, H., Rupar, C.A., de Wagenaar, N.P., Wu, K.M., Lahiry, P., Pazour, G.J., Nelson, S.F., Hegele, R.A., Roepman, R., Kayserili, H., Venkatesh, B., Siu, V.M., Reversade, B., and Arts, H.H. (2016) A novel ICK mutation causes ciliary disruption and lethal endocrine-cerebro-osteodysplasia syndrome. *Cilia* **5**, 8
32. Okamoto, S., Chaya, T., Omori, Y., Kuwahara, R., Kubo, S., Sakaguchi, H., and Furukawa, T. (2017) Ick ciliary kinase is essential for planar cell polarity formation in inner ear hair cells and hearing function. *J. Neurosci.* **37**, 2073–2085
33. Berman, S.A., Wilson, N.F., Haas, N.A., and Lefebvre, P.A. (2003) A novel MAP kinase regulates flagellar length in *Chlamydomonas*. *Curr. Biol.* **13**, 1145–1149
34. Bengs, F., Scholz, A., Kuhn, D., and Wiese, M. (2005) LmxMPK9, a mitogen-activated protein kinase homologue affects flagellar length in *Leishmania mexicana*. *Mol. Microbiol.* **55**, 1606–1615
35. Burghoorn, J., Dekkers, M.P., Rademakers, S., de Jong, T., Willemsen, R., and Jansen, G. (2007) Mutation of the MAP kinase DYF-5 affects docking and undocking of kinesin-2 motors and reduces their speed in the cilia of *Caenorhabditis elegans*. *Proc. Natl. Acad. Sci. USA.* **104**, 7157–7162
36. Maurya, A.K., Rogers, T., and Sengupta, P. (2019) A CCRK and a MAK kinase modulate cilia branching and length via regulation of axonemal microtubule dynamics in *Caenorhabditis elegans*. *Curr. Biol.* **29**, 1286–1300 e1284
37. Jiang, Y.Y., Maier, W., Baumeister, R., Minevich, G., Joachimiak, E., Wloga, D., Ruan, Z., Kannan, N., Bocarro, S., Bahraini, A., Vasudevan, K.K., Lehtreck, K., Orias, E., and Gaertig, J. (2019) LF4/MOK and a CDK-related kinase regulate the number and length of cilia in tetrahymena. *PLoS Genet.* **15**, e1008099
38. Oh, Y.S., Wang, E.J., Gailey, C.D., Brautigan, D.L., Allen, B.L., and Fu, Z. (2019) Ciliopathy-associated protein kinase ICK requires its non-catalytic carboxyl-terminal domain for regulation of ciliogenesis. *Cells* **8**, 677
39. Fu, Z., Larson, K.A., Chitta, R.K., Parker, S.A., Turk, B.E., Lawrence, M.W., Kaldis, P., Galaktionov, K., Cohn, S.M., Shabanowitz, J., Hunt, D.F., and Sturgill, T.W. (2006) Identification of yin-yang regulators and a phosphorylation consensus for male germ cell-associated kinase (MAK)-related kinase. *Mol. Cell. Biol.* **26**, 8639–8654
40. Gailey, C.D., Wang, E.J., Jin, L., Ahmadi, S., Brautigan, D.L., Li, X., Xu, W., Scott, M.M., and Fu, Z. (2021) Phosphosite T674A mutation in kinesin family member 3A fails to reproduce tissue and ciliary defects characteristic of CILK1 loss of function. *Dev. Dyn.* **250**, 263–273
41. Liang, Y., Pang, Y., Wu, Q., Hu, Z., Han, X., Xu, Y., Deng, H., and Pan, J. (2014) FLA8/KIF3B phosphorylation regulates kinesin-II interaction with IFT-B to control IFT entry and turnaround. *Dev. Cell.* **30**, 585–597
42. Ozgul, R.K., Siemiatkowska, A.M., Yucel, D., Myers, C.A., Collin, R.W., Zonneveld, M.N., Beryozkin, A., Banin, E., Hoyng, C.B., van den Born, L.I., European Retinal Disease, C., Bose, R., Shen, W., Sharon, D., Cremers, F.P., Klevering, B.J., den Hollander, A.I., and Corbo, J.C., European Retinal Disease Consortium (2011) Exome sequencing and

- cis-regulatory mapping identify mutations in MAK, a gene encoding a regulator of ciliary length, as a cause of retinitis pigmentosa. *Am. J. Hum. Genet.* **89**, 253–264
43. Tucker, B.A., Scheetz, T.E., Mullins, R.F., DeLuca, A.P., Hoffmann, J.M., Johnston, R.M., Jacobson, S.G., Sheffield, V.C., and Stone, E.M. (2011) Exome sequencing and analysis of induced pluripotent stem cells identify the cilia-related gene male germ cell-associated kinase (MAK) as a cause of retinitis pigmentosa. *Proc. Natl. Acad. Sci. USA* **108**, E569–576
 44. Fu, Z., Gailey, C.D., Wang, E.J., and Brautigan, D.L. (2019) Ciliogenesis associated kinase 1: targets and functions in various organ systems. *FEBS Lett.* **593**, 2990–3002
 45. Lahiry, P., Wang, J., Robinson, J.F., Turowec, J.P., Litchfield, D.W., Lanktree, M.B., Gloor, G.B., Puffenberger, E.G., Strauss, K.A., Martens, M.B., Ramsay, D.A., Rupar, C.A., Siu, V., and Hegele, R.A. (2009) A multiplex human syndrome implicates a key role for intestinal cell kinase in development of central nervous, skeletal, and endocrine systems. *Am. J. Hum. Genet.* **84**, 134–147
 46. Bailey, J.N., de Nijs, L., Bai, D., Suzuki, T., Miyamoto, H., Tanaka, M., Patterson, C., Lin, Y.C., Medina, M.T., Alonso, M.E., Serratosa, J.M., Duron, R.M., Nguyen, V.H., Wight, J.E., Martinez-Juarez, I.E., Ochoa, A., Jara-Prado, A., Guilhoto, L., Molina, Y., Yacubian, E.M., Lopez-Ruiz, M., Inoue, Y., Kaneko, S., Hirose, S., Osawa, M., Oguni, H., Fujimoto, S., Grisar, T.M., Stern, J.M., Yamakawa, K., Lakaye, B., and Delgado-Escueta, A.V. (2018) Variant intestinal-cell kinase in juvenile myoclonic epilepsy. *N Engl. J. Med.* **378**, 1018–1028
 47. Wang, E.J., Gailey, C.D., Brautigan, D.L., and Fu, Z. (2020) Functional alterations in ciliogenesis-associated kinase 1 (CILK1) that result from mutations linked to juvenile myoclonic epilepsy. *Cells* **9**, 694
 48. Yang, Y., Roine, N., and Makela, T.P. (2013) CCRK depletion inhibits glioblastoma cell proliferation in a cilium-dependent manner. *EMBO Rep.* **14**, 741–747
 49. Snouffer, A., Brown, D., Lee, H., Walsh, J., Lupu, F., Norman, R., Lehtreck, K., Ko, H.W., and Eggenschwiler, J. (2017) Cell cycle-related kinase (CCRK) regulates ciliogenesis and Hedgehog signaling in mice. *PLoS Genet.* **13**, e1006912
 50. Lupu, F.I., Burnett, J.B., and Eggenschwiler, J.T. (2018) Cell cycle-related kinase regulates mammalian eye development through positive and negative regulation of the Hedgehog pathway. *Dev. Biol.* **434**, 24–35
 51. Lee, H., and Ko, H.W. (2020) Cell cycle-related kinase is a crucial regulator for ciliogenesis and Hedgehog signaling in embryonic mouse lung development. *BMB Rep.* **53**, 367–372
 52. Tam, L.W., Wilson, N.F., and Lefebvre, P.A. (2007) A CDK-related kinase regulates the length and assembly of flagella in *Chlamydomonas*. *J. Cell Biol.* **176**, 819–829
 53. Phirke, P., Efimenko, E., Mohan, S., Burghoorn, J., Crona, F., Bakhoun, M.W., Trieb, M., Schuske, K., Jorgensen, E.M., Piasecki, B.P., Leroux, M.R., and Swoboda, P. (2011) Transcriptional profiling of *C. elegans* DAF-19 uncovers a ciliary base-associated protein and a CDK/CCRK/LF2p-related kinase required for intraflagellar transport. *Dev. Biol.* **357**, 235–247
 54. Wang, Y., Ren, Y., and Pan, J. (2019) Regulation of flagellar assembly and length in *Chlamydomonas* by LF4, a MAPK-related kinase. *Faseb J.* **33**, 6431–6441
 55. Neugebauer, J.M., Amack, J.D., Peterson, A.G., Bisgrove, B.W., and Yost, H.J. (2009) FGF signalling during embryo development regulates cilia length in diverse epithelia. *Nature* **458**, 651–654
 56. Martin, L., Kaci, N., Estivals, V., Goudin, N., Garfa-Traore, M., Benoist-Lasselien, C., Dambroise, E., and Legeai-Mallet, L. (2018) Constitutively-active FGFR3 disrupts primary cilium length and IFT20 trafficking in various chondrocyte models of achondroplasia. *Hum. Mol. Genet.* **27**, 1–13
 57. Kunova Bosakova, M., Varecha, M., Hampl, M., Duran, I., Nita, A., Buchtova, M., Dosedelova, H., Machat, R., Xie, Y., Ni, Z., Martin, J.H., Chen, L., Jansen, G., Krakow, D., and Krejci, P. (2018) Regulation of ciliary function by fibroblast growth factor signaling identifies FGFR3-related disorders achondroplasia and thanatophoric dysplasia as ciliopathies. *Hum. Mol. Genet.* **27**, 1093–1105
 58. Kunova Bosakova, M., Nita, A., Gregor, T., Varecha, M., Gudernova, I., Fafilek, B., Barta, T., Basheer, N., Abraham, S.P., Balek, L., Tomanova, M., Fialova Kucerova, J., Bosak, J., Potesil, D., Zieba, J., Song, J., Konik, P., Park, S., Duran, I., Zdrahal, Z., Smajs, D., Jansen, G., Fu, Z., Ko, H.W., Hampl, A., Trantirek, L., Krakow, D., and Krejci, P. (2019) Fibroblast growth factor receptor influences primary cilium length through an interaction with intestinal cell kinase. *Proc. Natl. Acad. Sci. USA* **116**, 4316–4325
 59. Jensen, V.L., and Leroux, M.R. (2017) Gates for soluble and membrane proteins, and two trafficking systems (IFT and LIFT), establish a dynamic ciliary signaling compartment. *Curr. Opin. Cell Biol.* **47**, 83–91
 60. Ismail, S.A., Chen, Y.X., Rusinova, A., Chandra, A., Bierbaum, M., Gremer, L., Triola, G., Waldmann, H., Bastiaens, P.I., and Wittinghofer, A. (2011) Arl2-GTP and Arl3-GTP regulate a GDI-like transport system for farnesylated cargo. *Nat. Chem. Biol.* **7**, 942–949
 61. Ismail, S.A., Chen, Y.X., Miertzschke, M., Vetter, I.R., Koerner, C., and Wittinghofer, A. (2012) Structural basis for Arl3-specific release of myristoylated ciliary cargo from UNC119. *Embo J.* **31**, 4085–4094
 62. Wright, K.J., Baye, L.M., Olivier-Mason, A., Mukhopadhyay, S., Sang, L., Kwong, M., Wang, W., Pretorius, P.R., Sheffield, V.C., Sengupta, P., Slusarski, D.C., and Jackson, P.K. (2011) An ARL3-UNC119-RP2 GTPase cycle targets myristoylated NPHP3 to the primary cilium. *Genes Dev.* **25**, 2347–2360
 63. Zhang, H., Constantine, R., Vorobiev, S., Chen, Y., Seetharaman, J., Huang, Y.J., Xiao, R., Montelione, G.T., Gerstner, C.D., Davis, M.W., Inana, G., Whitby, F.G., Jorgensen, E.M., Hill, C.P., Tong, L., and Baehr, W. (2011) UNC119 is required for G protein trafficking in sensory neurons. *Nat. Neurosci.* **14**, 874–880
 64. Gotthardt, K., Lokaj, M., Koerner, C., Falk, N., Giebl, A., and Wittinghofer, A. (2015) A G-protein activation cascade from Arl13B to Arl3 and implications for ciliary targeting of lipidated proteins. *Elife* **4**, e11859
 65. Veltel, S., Gasper, R., Eisenacher, E., and Wittinghofer, A. (2008) The retinitis pigmentosa 2 gene product is a GTPase-activating protein for Arf-like 3. *Nat. Struct. Mol. Biol.* **15**, 373–380

66. Evans, R.J., Schwarz, N., Nagel-Wolfrum, K., Wolfrum, U., Hardcastle, A.J., and Cheetham, M.E. (2010) The retinitis pigmentosa protein RP2 links pericentriolar vesicle transport between the Golgi and the primary cilium. *Hum. Mol. Genet.* **19**, 1358–1367
67. Brann, M.R., and Cohen, L.V. (1987) Diurnal expression of transducin mRNA and translocation of transducin in rods of rat retina. *Science* **235**, 585–587
68. Philp, N.J., Chang, W., and Long, K. (1987) Light-stimulated protein movement in rod photoreceptor cells of the rat retina. *FEBS Lett.* **225**, 127–132
69. Whelan, J.P., and McGinnis, J.F. (1988) Light-dependent subcellular movement of photoreceptor proteins. *J. Neurosci. Res.* **20**, 263–270
70. Organisciak, D.T., Xie, A., Wang, H.M., Jiang, Y.L., Darrow, R.M., and Donoso, L.A. (1991) Adaptive changes in visual cell transduction protein levels: effect of light. *Exp. Eye Res.* **53**, 773–779
71. Sokolov, M., Lyubarsky, A.L., Strissel, K.J., Savchenko, A.B., Govardovskii, V.I., Pugh, E.N., Jr., and Arshavsky, V.Y. (2002) Massive light-driven translocation of transducin between the two major compartments of rod cells: a novel mechanism of light adaptation. *Neuron* **34**, 95–106.
72. Kerov, V., Rubin, W.W., Natochin, M., Melling, N.A., Burns, M.E., and Artemyev, N.O. (2007) N-terminal fatty acylation of transducin profoundly influences its localization and the kinetics of photoresponse in rods. *J. Neurosci.* **27**, 10270–10277
73. Peng, Y.W., Zallocchi, M., Wang, W.M., Delimont, D., and Cosgrove, D. (2011) Moderate light-induced degeneration of rod photoreceptors with delayed transducin translocation in shaker1 mice. *Invest. Ophthalmol. Vis. Sci.* **52**, 6421–6427
74. Tian, M., Wang, W., Delimont, D., Cheung, L., Zallocchi, M., Cosgrove, D., and Peng, Y.W. (2014) Photoreceptors in whirler mice show defective transducin translocation and are susceptible to short-term light/dark changes-induced degeneration. *Exp. Eye Res.* **118**, 145–153
75. Kerov, V., and Artemyev, N.O. (2011) Diffusion and light-dependent compartmentalization of transducin. *Mol. Cell. Neurosci.* **46**, 340–346
76. Majumder, A., Pahlberg, J., Boyd, K.K., Kerov, V., Kolandaivelu, S., Ramamurthy, V., Sampath, A.P., and Artemyev, N.O. (2013) Transducin translocation contributes to rod survival and enhances synaptic transmission from rods to rod bipolar cells. *Proc. Natl. Acad. Sci. USA* **110**, 12468–12473
77. Gopalakrishna, K.N., Doddapuneni, K., Boyd, K.K., Masuho, I., Martemyanov, K.A., and Artemyev, N.O. (2011) Interaction of transducin with uncoordinated 119 protein (UNC119): implications for the model of transducin trafficking in rod photoreceptors. *J. Biol. Chem.* **286**, 28954–28962
78. Ishiba, Y., Higashide, T., Mori, N., Kobayashi, A., Kubota, S., McLaren, M.J., Satoh, H., Wong, F., and Inana, G. (2007) Targeted inactivation of synaptic HRG4 (UNC119) causes dysfunction in the distal photoreceptor and slow retinal degeneration, revealing a new function. *Exp. Eye Res.* **84**, 473–485
79. Kobayashi, A., Higashide, T., Hamasaki, D., Kubota, S., Sakuma, H., An, W., Fujimaki, T., McLaren, M.J., Weleber, R.G., and Inana, G. (2000) HRG4 (UNC119) mutation found in cone-rod dystrophy causes retinal degeneration in a transgenic model. *Invest. Ophthalmol. Vis. Sci.* **41**, 3268–3277
80. Mori, N., Ishiba, Y., Kubota, S., Kobayashi, A., Higashide, T., McLaren, M.J., and Inana, G. (2006) Truncation mutation in HRG4 (UNC119) leads to mitochondrial ANT-1-mediated photoreceptor synaptic and retinal degeneration by apoptosis. *Invest. Ophthalmol. Vis. Sci.* **47**, 1281–1292
81. Hagiwara, K., Wada, A., Katadae, M., Ito, M., Ohya, Y., Casey, P.J., and Fukada, Y. (2004) Analysis of the molecular interaction of the farnesyl moiety of transducin through the use of a photoreactive farnesyl analogue. *Biochemistry* **43**, 300–309
82. Zhang, H., Li, S., Doan, T., Rieke, F., Detwiler, P.B., Frederick, J.M., and Baehr, W. (2007) Deletion of PrBP/delta impedes transport of GRK1 and PDE6 catalytic subunits to photoreceptor outer segments. *Proc. Natl. Acad. Sci. USA* **104**, 8857–8862
83. Anant, J.S., Ong, O.C., Xie, H.Y., Clarke, S., O'Brien, P.J., and Fung, B.K. (1992) In vivo differential prenylation of retinal cyclic GMP phosphodiesterase catalytic subunits. *J. Biol. Chem.* **267**, 687–690
84. Inglese, J., Glickman, J.F., Lorenz, W., Caron, M.G., and Lefkowitz, R.J. (1992) Isoprenylation of a protein kinase. Requirement of farnesylation/alpha-carboxyl methylation for full enzymatic activity of rhodopsin kinase. *J. Biol. Chem.* **267**, 1422–1425
85. Anant, J.S., and Fung, B.K. (1992) In vivo farnesylation of rat rhodopsin kinase. *Biochem. Biophys. Res. Commun.* **183**, 468–473
86. Hanke-Gogokhia, C., Wu, Z., Gerstner, C.D., Frederick, J.M., Zhang, H., and Baehr, W. (2016) Arf-like Protein 3 (ARL3) regulates protein trafficking and ciliogenesis in mouse photoreceptors. *J. Biol. Chem.* **291**, 7142–7155
87. Strom, S.P., Clark, M.J., Martinez, A., Garcia, S., Abelazeem, A.A., Matynia, A., Parikh, S., Sullivan, L.S., Bowne, S.J., Daiger, S.P., and Gorin, M.B. (2016) De novo occurrence of a variant in ARL3 and apparent autosomal dominant transmission of retinitis pigmentosa. *PLoS One* **11**, e0150944
88. Hanke-Gogokhia, C., Wu, Z., Sharif, A., Yazigi, H., Frederick, J.M., and Baehr, W. (2017) The guanine nucleotide exchange factor Arf-like protein 13b is essential for assembly of the mouse photoreceptor transition zone and outer segment. *J. Biol. Chem.* **292**, 21442–21456
89. Dilan, T.L., Moye, A.R., Salido, E.M., Saravanan, T., Kolandaivelu, S., Goldberg, A.F.X., and Ramamurthy, V. (2019) ARL13B, a Joubert syndrome-associated protein, is critical for retinogenesis and elaboration of mouse photoreceptor outer segments. *J. Neurosci.* **39**, 1347–1364
90. Cantagrel, V., Silhavy, J.L., Bielas, S.L., Swistun, D., Marsh, S.E., Bertrand, J.Y., Audollent, S., Attié-Bitach, T., Holden, K.R., Dobyns, W.B., Traver, D., Al-Gazali, L., Ali, B.R., Lindner, T.H., Caspary, T., Otto, E.A., Hildebrandt, F., Glass, I.A., Logan, C.V., Johnson, C.A., Bennett, C., Brancati, F., International Joubert Syndrome Related Disorders Study, G., Valente, E.M., Woods, C.G., and Gleeson, J.G., International Joubert Syndrome Related Disorders Study Group (2008) Mutations in the cilia gene ARL13B lead to the classical form of Joubert syndrome. *Am. J. Hum. Genet.* **83**, 170–179
91. Thomas, S., Cantagrel, V., Mariani, L., Serre, V., Lee, J.-E., Elkhartoufi, N., de Lonlay, P., Desguerre, I., Munnich, A., Boddaert, N., Lyonnet, S., Vekemans, M., Lisgo, S.N., Caspary, T., Gleeson, J., and Attié-Bitach, T. (2015) Identification of a novel ARL13B variant in a Joubert syndrome-affected

- patient with retinal impairment and obesity. *Eur. J. Hum. Genet.* **23**, 621–627
92. Zhang, H., Hanke-Gogokhia, C., Jiang, L., Li, X., Wang, P., Gerstner, C.D., Frederick, J.M., Yang, Z., and Baehr, W. (2015) Mistrafficking of prenylated proteins causes retinitis pigmentosa 2. *FASEB J.* **29**, 932–942
 93. Schwahn, U., Lenzner, S., Dong, J., Feil, S., Hinzmann, B., van Duijnhoven, G., Kirschner, R., Hemberger, M., Bergen, A.A., Rosenberg, T., Pinckers, A.J., Fundele, R., Rosenthal, A., Cremers, F.P., Ropers, H.H., and Berger, W. (1998) Positional cloning of the gene for X-linked retinitis pigmentosa 2. *Nat. Genet.* **19**, 327–332
 94. Jayasundera, T., Branham, K.E., Othman, M., Rhoades, W.R., Karoukis, A.J., Khanna, H., Swaroop, A., and Heckenlively, J.R. (2010) RP2 phenotype and pathogenetic correlations in X-linked retinitis pigmentosa. *Arch. Ophthalmol.* **128**, 915–923
 95. Dandekar, S.S., Ebenezer, N.D., Grayson, C., Chapple, J.P., Egan, C.A., Holder, G.E., Jenkins, S.A., Fitzke, F.W., Cheetham, M.E., Webster, A.R., and Hardcastle, A.J. (2004) An atypical phenotype of macular and peripapillary retinal atrophy caused by a mutation in the RP2 gene. *Br. J. Ophthalmol.* **88**, 528–532
 96. Petroski, M.D., and Deshaies, R.J. (2005) Function and regulation of cullin-RING ubiquitin ligases. *Nat. Rev. Mol. Cell Biol.* **6**, 9–20
 97. Sarikas, A., Hartmann, T., and Pan, Z.Q. (2011) The cullin protein family. *Genome Biol.* **12**, 220
 98. Pan, Z.Q., Kentsis, A., Dias, D.C., Yamoah, K., and Wu, K. (2004) Nedd8 on cullin: building an expressway to protein destruction. *Oncogene* **23**, 1985–1997
 99. Dhanoa, B.S., Cogliati, T., Satish, A.G., Bruford, E.A., and Friedman, J.S. (2013) Update on the Kelch-like (KLHL) gene family. *Hum. Genomics* **7**, 13
 100. Soucy, T.A., Smith, P.G., Milhollen, M.A., Berger, A.J., Gavin, J.M., Adhikari, S., Brownell, J.E., Burke, K.E., Cardin, D.P., Critchley, S., Cullis, C.A., Doucette, A., Garnsey, J.J., Gaulin, J.L., Gershman, R.E., Lublinsky, A.R., McDonald, A., Mizutani, H., Narayanan, U., Olhava, E.J., Peluso, S., Rezaei, M., Sintchak, M.D., Talreja, T., Thomas, M.P., Traore, T., Vyskocil, S., Weatherhead, G.S., Yu, J., Zhang, J., Dick, L.R., Claiborne, C.F., Rolfe, M., Bolen, J.B., and Langston, S.P. (2009) An inhibitor of NEDD8-activating enzyme as a new approach to treat cancer. *Nature* **458**, 732–736
 101. Trojan, P., Rausch, S., Giessl, A., Klemm, C., Krause, E., Pulvermuller, A., and Wolfrum, U. (2008) Light-dependent CK2-mediated phosphorylation of centrins regulates complex formation with visual G-protein. *Biochim. Biophys. Acta* **1783**, 1248–1260
 102. Klee, C.B., Crouch, T.H., and Krinks, M.H. (1979) Calcineurin: a calcium- and calmodulin-binding protein of the nervous system. *Proc. Natl. Acad. Sci. USA* **76**, 6270–6273
 103. Klee, C.B., Ren, H., and Wang, X. (1998) Regulation of the calmodulin-stimulated protein phosphatase, calcineurin. *J. Biol. Chem.* **273**, 13367–13370
 104. Chaya, T., Tsutsumi, R., Varner, L.R., Maeda, Y., Yoshida, S., and Furukawa, T. (2019) Cul3-Klhl18 ubiquitin ligase modulates rod transducin translocation during light-dark adaptation. *Embo J.* **38**, e101409
 105. Parmeggiani, F., Sato, G., De Nadai, K., Romano, M.R., Binotto, A., and Costagliola, C. (2011) Clinical and rehabilitative management of retinitis pigmentosa: up-to-date. *Curr. Genomics* **12**, 250–259
 106. Schick, T., Ersoy, L., Lechanteur, Y.T., Saksens, N.T., Hoyng, C.B., den Hollander, A.I., Kirchhof, B., and Fauser, S. (2016) History of sunlight exposure is a risk factor for age-related macular degeneration. *Retina* **36**, 787–790
 107. Mitchell, P., Liew, G., Gopinath, B., and Wong, T.Y. (2018) Age-related macular degeneration. *Lancet* **392**, 1147–1159
 108. Marquioni-Ramella, M.D., and Suburo, A.M. (2015) Photo-damage, photo-protection and age-related macular degeneration. *Photochem. Photobiol. Sci.* **14**, 1560–1577
 109. Kassai, H., Aiba, A., Nakao, K., Nakamura, K., Katsuki, M., Xiong, W.H., Yau, K.W., Imai, H., Shichida, Y., Satomi, Y., Takao, T., Okano, T., and Fukada, Y. (2005) Farnesylation of retinal transducin underlies its translocation during light adaptation. *Neuron* **47**, 529–539
 110. Manning, G., Whyte, D.B., Martinez, R., Hunter, T., and Sudarsanam, S. (2002) The protein kinase complement of the human genome. *Science* **298**, 1912–1934