

REVIEW

Open Access

Intraflagellar transport complex structure and cargo interactions

Sagar Bhogaraju¹, Benjamin D Engel² and Esben Lorentzen^{1*}

Abstract

Intraflagellar transport (IFT) is required for the assembly and maintenance of cilia, as well as the proper function of ciliary motility and signaling. IFT is powered by molecular motors that move along the axonemal microtubules, carrying large complexes of IFT proteins that travel together as so-called trains. IFT complexes likely function as adaptors that mediate interactions between anterograde/retrograde motors and ciliary cargoes, facilitating cargo transport between the base and tip of the cilium. Here, we provide an up-to-date review of IFT complex structure and architecture, and discuss how interactions with cargoes and motors may be achieved.

Keywords: Intraflagellar transport, Cilium, IFT, IFT complex, IFT cargo

Review

Twenty years ago, Kozminsky and colleagues first described intraflagellar transport (IFT) as a motility in the *Chlamydomonas* flagellum that is distinct from flagellar beating [1]. IFT trains were observed by electron microscopy to be linear arrays of electron-dense particles spanning the distance between the outer doublet microtubules and the flagellar membrane. Following the discovery of IFT, biochemical purification of native IFT complexes from *Chlamydomonas* revealed 15 polypeptides that organize into two IFT sub-complexes, known as IFT-A and IFT-B [2,3]. IFT polypeptide orthologues were also found in mice [4,5], suggesting that IFT proteins are largely conserved. Subsequent studies identified additional IFT proteins, bringing the current IFT protein count up to 20 [5-11]. Mutations in IFT proteins have been shown to cause several ciliopathies [12-22]. The genetic deletion of an entire IFT protein often leads to a general defect in cilia assembly (presumably due to IFT complex disruption), making it difficult to assess the specific functions of individual IFT proteins from mutant phenotypes alone [8,23-31]. Thus, a more complete understanding of IFT protein function in ciliogenesis, including cargo and motor interactions, will require detailed molecular and structural studies of IFT complexes.

Structural investigations of IFT complexes have been limited so far to electron tomographic reconstructions of IFT particles *in situ* [32] and the high-resolution crystal structure of the IFT25/27 sub-complex [33]. However, the overall architecture of the IFT complex is starting to take shape, largely as a result of biochemical studies [25,26,34,35]. In this review we attempt to partition IFT proteins into principal domains (PD) and auxiliary domains (AD) based on the current literature. Whereas PD mutations lead to IFT complex destabilization with general ciliogenesis phenotypes, AD mutations may facilitate the study of specific IFT protein functionality. Such a division may assist in designing experiments to probe the roles of individual IFT proteins in cilium formation and function.

The intraflagellar transport complex: a protein-protein interaction platform?

Bioinformatic analysis of IFT proteins predicts a large number of potential protein-protein interaction domains such as tetratricopeptide repeats (TPRs), WD40 β -propellers and coiled-coils [36-39]. Strikingly, with the exception of the two small GTPases IFT22 and IFT27, none of the other IFT proteins are predicted to have enzymatic activity. The prediction is thus that the IFT complex forms a large platform with multiple protein interaction sites that allows binding to molecular motors as well as ciliary cargoes.

Structure prediction using the HHpred server [40] revealed that most IFT proteins likely contain multiple

* Correspondence: lorentze@biochem.mpg.de

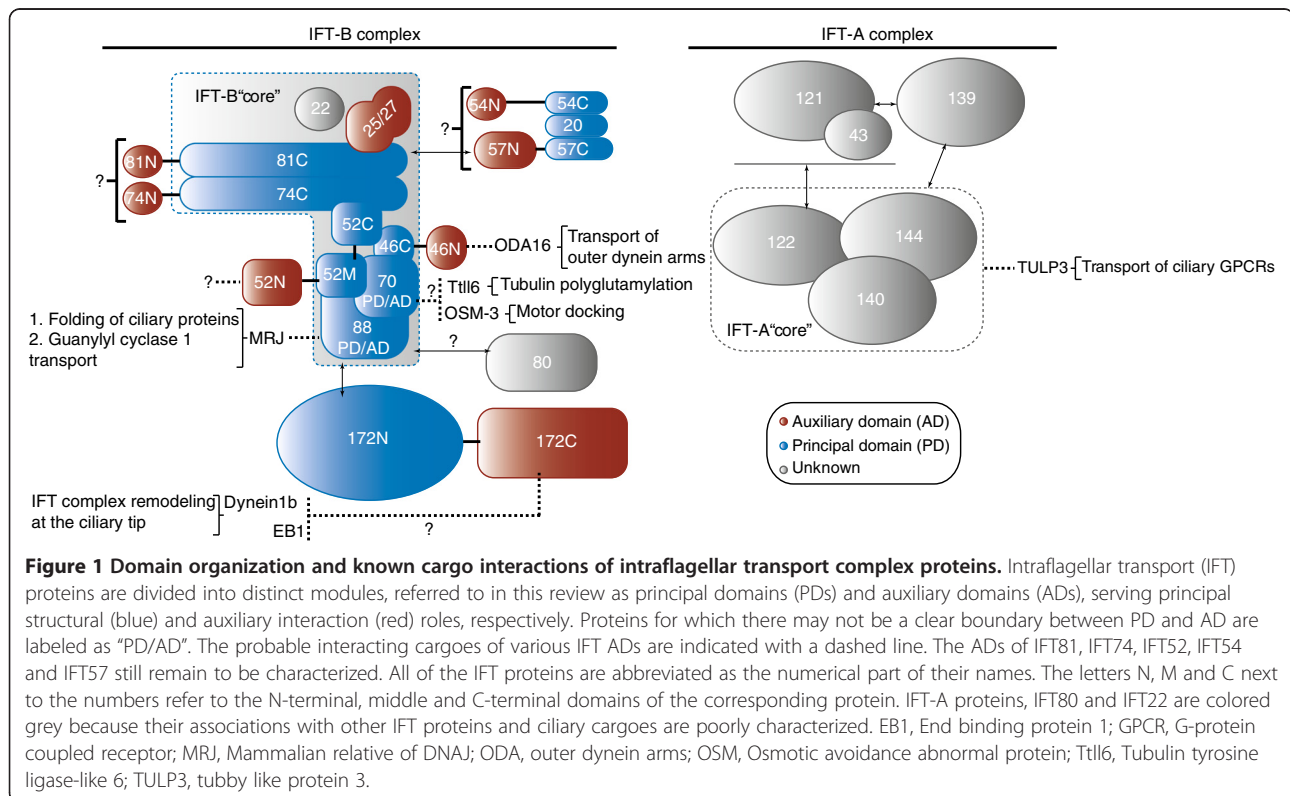
¹Department of Structural Cell Biology, Max-Planck-Institute of Biochemistry, Am Klopferspitz 18, D-82152 Martinsried, Germany

Full list of author information is available at the end of the article

domains [39]. Limited proteolysis on *in vitro* reconstituted IFT complexes demonstrated that only a subset of these domains are required for IFT complex formation, indicating that numerous domains are available to interact with other binding partners such as ciliary cargoes or motors [35]. Most IFT proteins can therefore be divided into PDs and ADs as described above (Figure 1). The main function of PDs is to provide structural stability, and thus they are well conserved in protein sequence to ensure the integrity of IFT complex formation. However, most IFT protein domains not required for IFT complex stability (the ADs) are also highly conserved in sequence, likely reflecting important functions such as ciliary cargo interactions. A good example of the PD/AD division is IFT46, a core component of IFT-B, where only the IFT46 C-terminal domain is required for the stability of the IFT complex via interaction with the C-terminal domain of IFT52 [25,35], while the N-terminal domain is involved in the ciliary transport of outer dynein arms (ODAs) [24,41,42]. Similarly, IFT52 interacts directly with at least four different IFT proteins (IFT74/81, IFT46, IFT70 and IFT88) via its middle and C-terminal domains, while the conserved N-terminal domain is not required for IFT-B complex formation and thus likely constitutes an AD [25,35]. The N-terminal domain of IFT74 is also not required for IFT-B core complex formation and may constitute

an AD [35]. The peripheral IFT proteins IFT54 and IFT57 both have predicted coiled-coil domains at the C-termini that interact with IFT20 [43-45]. However, the N-terminal regions of both IFT57 and IFT54 are predicted to be alpha helical domains that could constitute ADs [39] (Figure 1).

It is important to note that while the PD/AD boundary of some IFT proteins is well defined, this is not the case for all IFT proteins. In particular, TPR domain-containing proteins such as IFT70 and IFT88 may possess a single structural module that functions as both a PD and an AD (Figure 1). Another example is IFT25 and the small GTPase IFT27, which form a stable heterodimer that can be considered as a single structural module [33]. While the IFT25/27 heterodimer directly binds the “core” IFT74/81 complex [35], it also contains a conserved surface patch in close proximity to the GTPase active site of IFT27 that may interact with a yet unidentified binding partner in a nucleotide-state-dependent manner [33]. Interestingly, IFT25 knockout mice show no ciliogenesis defects but die at birth due to sonic hedgehog (Shh) signaling dysfunction [46]. This indicates that the IFT25/27 sub-complex is not needed for the stability of the IFT complex and may function in the IFT of Shh signaling components. Additionally, IFT25 and IFT27 are not present in *Caenorhabditis elegans* and *Drosophila melanogaster* [10,38]. Thus, IFT25/27 may be defined as an AD module (Figure 1).



Ciliary targeting sequences

Proteins that localize to subcellular compartments such as mitochondria or the nucleus have distinct sequence motifs (known as cellular ZIP codes) that specifically target them to their respective organelles [47]. Although the cilium is topologically equivalent to the cytoplasm, there are transition zone structures at the ciliary base that prevent random diffusion of both soluble and membrane-bound macromolecules into the cilium [48-56]. As approximately 600 different proteins reside within the cilium [57], it seems likely that one or more ZIP codes also exist for ciliary targeting [58].

The (F/Y/W)R motif

One of the earliest reports of a ciliary targeting sequence (CTS) was the identification of a phenylalanine-arginine (FR) motif in the C-terminal cytoplasmic regions of *C. elegans* olfactory receptor proteins ODR-10 and STR-1 [59]. Deletion of this FR motif from ODR-10 and STR-1 resulted in dispersed localization of the receptors in the cell body, indicating that the FR motif is required for ciliary localization. This (F/Y/W)R motif is conserved in several ciliary G-protein coupled receptors (GPCRs) including somatostatin receptor 3 (SSTR3), serotonin receptor 6 (5-HTR6) and rhodopsin, suggesting a widely prevalent and conserved mechanism of targeting GPCRs to the cilium [59]. A similar motif in mammalian Smoothed (smo) was also shown to be required for localization to the cilium [60]. However, several GPCRs that contain (F/Y/W)R motifs do not localize to cilia, indicating that the ciliary targeting of GPCR proteins is more complex. Inspection of the rhodopsin crystal structure reveals that an equivalent residue (F313 of alpha-helix VIII) [61], identified to be a part of the (F/Y/W)R motif in the other GPCRs, is buried within the hydrophobic core of the protein and hence may be necessary for proper protein folding. This suggests that mislocalization of ciliary GPCRs upon mutation of the (F/Y/W)R motif may be an effect of compromised structural integrity of the GPCR fold rather than a primary defect in ciliary targeting. It is thus not surprising that different CTSs have been identified in several ciliary GPCRs including SSTR3, 5-HTR6 and rhodopsin, as described in the following sections.

The Ax(S/A)xQ motif

Comparative sequence conservation analysis of ciliary and non-ciliary GPCRs revealed a different consensus amino acid sequence, Ax(S/A)xQ (where x denotes any amino acid), in the third intracellular loop of ciliary GPCRs [62]. Mutating the conserved A or Q in this motif resulted in the mislocalization of SSTR3 and 5-HTR6 [62]. Conversely, the chimeric non-ciliary GPCR Htr7 with this

motif inserted into its third intracellular loop showed markedly increased ciliary localization [62]. Recently, a similar signal sequence was found in the third intracellular loop of another ciliary GPCR, melanin-concentrating hormone receptor 1 [63]. These results indicate that the Ax(S/A)xQ motif is both necessary and sufficient for the localization of these GPCRs. The mouse GPCR Gpr161 was also shown to contain a CTS ((I/V)KARK) in its third intracellular loop that is both necessary and sufficient for localization to cilia [64]. Interestingly, this CTS is different from the Ax(S/A)xQ motif described above, suggesting that the third intracellular loops of different GPCRs may contain distinct sequence motifs that confer ciliary localization.

The VxPx motif

In addition to the (F/Y/W)R motif described above, rhodopsin was shown to contain a VxPx motif at its cytoplasmic C-terminus that serves as a CTS [65,66]. The Ca²⁺ ion channel polycystin-2 (PC2) also has an N-terminal RVxP motif that is required for its ciliary localization [67], and polycystin-1 (PC1), a direct interacting partner of PC2, contains a similar CTS (KVHPSSST) at its cytoplasmic C-terminus [68]. Thus, PC1, PC2 and rhodopsin share a common (K/R/Q)VxPx motif required for ciliary localization.

The KRKK NLS-like motif

Compared to the CTSs of membrane proteins, very little is known about the ciliary targeting of soluble proteins. Although there is increasing evidence that tubulin, ODAs and retrograde dynein motors are IFT cargoes [24,69,70], it is unknown how these soluble proteins are recognized by the IFT machinery. Recently, however, the KRKK motif was identified as a CTS in the C-terminal tail of the homodimeric anterograde IFT motor KIF-17 [71]. Remarkably, this CTS is very similar to the nuclear localization signal (NLS) recognized by importin-β2. Both importin-β2 and a Ran-GTP gradient, which are key to nucleo-cytoplasmic transport, also appear to be required for ciliary entry of KIF-17 [71,72]. Furthermore, retinitis pigmentosa 2 was also shown to depend on interaction with importin-β2 for ciliary entry [73]. Another study identified certain nucleoporins at the base of the cilium by immunofluorescence and immunogold electron microscopy [51], although this result remains to be verified. It is unclear at this point whether NLS-mediated ciliary entry is applicable to a broad range of other ciliary proteins.

How are ciliary targeting sequences recognized by the intraflagellar transport machinery?

Several lines of evidence suggest that many of the above mentioned membrane proteins are transported into the

cilium as IFT cargoes. Rhodopsin requires transport into the outer segment (OS) of photoreceptor cells via the connecting cilium [74], and mutations in IFT proteins or motors have been shown to affect the transport of rhodopsin, indicating a critical role for IFT in this process [4,43,75,76]. The ciliary membrane Transient Receptor Potential Vanilloid (TRPV) channels OSM-9 and OCR-2 undergo IFT-like movements within the cilia of *C. elegans* sensory neurons [77], and a fraction of *Chlamydomonas* PC2 also undergoes directed movement that is likely driven by IFT [78]. Furthermore, in *Chlamydomonas* IFT has been shown to be physically coupled to the movement of flagellar membrane glycoproteins in a Ca^{2+} -dependent manner [79]. However, a direct link between the CTSS of membrane proteins and their association with the IFT complex has not yet been demonstrated.

Mutations in IFT-A proteins are known to affect the transport of several membrane proteins including certain ciliary GPCRs [64,80,81]. The BBSome is a multi-protein complex associated with IFT that is also required for the traffic of several membrane proteins into and out of the cilium [82-87]. Interestingly, the domain organizations of the BBS proteins and the IFT-A proteins closely resemble those of the canonical membrane coating complexes (COPI, COPII and Clathrin) [37,38]. Despite being involved in different intracellular trafficking pathways, all of these complexes contain numerous predicted WD-40 β -propeller and TPR/ α -solenoid-like domains, suggesting that these systems evolved from a common ancestral trafficking machinery and may utilize similar transport mechanisms [37,38,83]. Intriguingly, in the case of clathrin-mediated vesicular transport, WD40 β -propeller domains are known to selectively bind unique cargo peptides [88]. It is possible that the WD40 β -propeller domains in the IFT-A complex and BBSome selectively interact with the CTSS of ciliary membrane proteins to facilitate their transport into the cilium. Further studies characterizing the IFT-A and BBSome WD40 β -propeller domains may yield insights into ciliary membrane protein targeting and traffic.

Intraflagellar transport complex-cargo interactions

Although several studies have provided indirect evidence for the association of the IFT complex with ciliary cargoes, proof of direct interactions between IFT proteins and cargoes remains scarce. One of the earliest pieces of evidence for an association between the IFT complex and ciliary cargo comes from the co-immunoprecipitation of IFT74 and IFT139 performed on the soluble fraction of *Chlamydomonas* flagella, which revealed that the IFT complex interacts with ciliary precursors such as dynein light chains, radial spokes, motors and tubulin [89]. Tubulin, a basic structural component of the axoneme, was also

shown to undergo IFT-like movement in *C. elegans* sensory neurons [69]. In the following sections we discuss the various reports describing direct and indirect associations between IFT proteins and ciliary cargo.

IFT88

Several studies suggest interactions between the TPR-protein IFT88 and ciliary cargo. Co-immunoprecipitation of IFT88 from retinal extracts revealed an association with rhodopsin [90]. Furthermore, IFT88 and rhodopsin were shown to undergo similar movement within the cilia of hTERT-RPE1 cells, indicating that IFT likely plays a direct role in the transport of rhodopsin into the OS of photoreceptor cells [75]. Yeast two-hybrid studies and *in vitro* pulldown assays identified a Dnaj member co-chaperone, MRJ, as a direct interacting partner of IFT88 [90]. GST-tagged MRJ was also shown to associate with the photoreceptor-specific membrane protein guanylyl cyclase 1 (GC1) in a co-immunoprecipitation from bovine retinal extracts. This interaction was further confirmed by *in vitro* pulldown experiments using GST-MRJ and a HIS-tagged cytosolic fragment of GC1. It is possible that MRJ aids in the transport of ciliary GC1 by serving as an adaptor between GC1 and IFT88. As an IFT cargo, MRJ may also cooperate with HSP70 in the folding of ciliary proteins. The mode of interaction between IFT88 and these potential ciliary cargoes is currently unknown.

IFT70

IFT70 is another protein in the IFT complex that is predicted to contain TPR structure. Available evidence suggests that DYF-1, the *C. elegans* orthologue of IFT70, is required for the association of IFT particles with the IFT motor OSM-3. Two motors in *C. elegans*, heterotrimeric kinesin-2 (also called kinesin-II) and homodimeric OSM-3, coordinate to drive anterograde transport [91,92]. While both kinesin-2 and OSM-3 propel IFT in the middle segment of the cilium at a speed of 0.7 $\mu\text{m/s}$, OSM-3 alone drives IFT in the distal segment of the cilium at an increased speed of 1.2 $\mu\text{m/s}$ [91,93]. OSM-3 mutants (*osm-3*) were defective in distal segment formation, while the speed of anterograde IFT in the middle segment decreased from 0.7 $\mu\text{m/s}$ to 0.5 $\mu\text{m/s}$ [91,93]. Interestingly, *dyf-1* mutants exhibited a similar phenotype to *osm-3* mutants and lacked OSM-3 movement, indicating that IFT70/DYF-1 is involved in docking IFT particles onto OSM-3 motors [93]. An additional study revealed that OSM-3 is in an auto-inhibitory state *in vitro* and hypothesized that interaction with IFT proteins is required for activation [94]. Surprisingly, however, purified DYF-1 did not activate OSM-3 *in vitro* [94], and it has been suggested that additional factors may be required [23].

The depletion of the zebrafish IFT70 orthologue, *fleeer*, resulted in the loss of axonemal tubulin polyglutamylation

and ultrastructural defects of the outer doublet microtubules (MTs) [95]. Expression of only the N-terminal catalytic domain (residues 1 to 505) of the TTLL6 tubulin polyglutamylase enzyme also resulted in the loss of axonemal polyglutamylation but, intriguingly, basal body tubulin in these cells remained polyglutamylated [95]. Thus, it is possible that the C-terminus of TTLL6 directs ciliary localization through an interaction with IFT70. As polyglutamylation is known to affect the function of motors *in vivo* [96-98], it is possible that the OSM-3 motor is sensitive to the loss of tubulin polyglutamylation, and hence the effect of IFT70 on OSM-3 transport activity could be an indirect one [95]. Direct interaction studies between IFT70, OSM-3 type motors and the TTLL6 enzyme will likely shed light on this relationship.

IFT46

IFT46 is a well studied IFT-B core protein with an assigned function in the IFT of ODAs [24,41]. A *Chlamydomonas* insertional null IFT46 mutant showed reduced levels of other IFT complex proteins and flagellar assembly defects, indicating that full length IFT46 is necessary for the stability of the IFT complex [24]. A partial suppressor mutation, presumably expressing a C-terminal fragment of the IFT46 protein, alleviated most of the flagellar assembly phenotypes caused by the full depletion of IFT46, restoring wild-type IFT protein levels and normal flagellar length [24]. However, electron microscopy revealed that the axoneme of this suppressor mutant specifically lacks ODAs. This indicates that the N-terminus of IFT46 is involved in the transport of ODAs, while the C-terminus is required for the stability of the IFT complex [24]. This notion is supported by sequence alignments of IFT46 proteins, which only show high sequence identity for the N-terminal part of IFT46 from organisms with motile cilia, likely a reflection of this domain's conserved role in ODA transport (data not shown). It was later observed that IFT46 directly binds to ODA16, an adaptor protein that bridges the IFT complex with ODAs [41,42]. Further molecular characterization of the IFT46-ODA16-ODA complex is necessary to understand how IFT46 and ODA16 specifically recognize ODAs as ciliary cargoes.

The IFT-A complex

Compared to the IFT-B complex, proteins of the IFT-A complex are not well characterized. Co-immunoprecipitation of LAP-tagged tubby like protein 3 (TULP3) from human RPE1 cell extract revealed that IFT-A proteins interact directly with TULP3 [80]. This interaction was further mapped to the IFT-A "core" complex that contains IFT140, IFT144 and IFT122 [80]. Interestingly, depletion of either IFT-A "core" components or TULP3

caused mislocalization of certain ciliary GPCRs. TULP3 contains a TUBBY domain at its C-terminus that binds phosphoinositides [99]. A TULP3 mutant (TULP3KR) that is defective in phosphoinositide binding affected the localization of ciliary GPCRs but was still able to interact with the IFT-A complex [80]. This indicates that TULP3 bridges the IFT-A complex and ciliary GPCRs, thus aiding in ciliary GPCR transport. Further studies are needed to dissect the TULP3 interaction with IFT-A, as well as the specific role of the TUBBY domain in recognizing ciliary GPCRs [64,100].

Intraflagellar transport complex-motor interactions

The interactions between IFT motors and IFT complexes are central to understanding how the bidirectional movement of IFT trains is regulated, particularly at the IFT turnaround zones at the ciliary base and tip [101]. As described above, IFT70 (with the help of additional factors) may mediate OSM-3 docking to IFT particles in *C. elegans*. However, the binding interactions between IFT complexes and the most evolutionarily conserved IFT motors, heterotrimeric kinesin-2 and cytoplasmic dynein 2, remain more elusive. Kinesin-2 appears to bind the IFT-A complex in *C. elegans*, and is only physically coupled to IFT-B and OSM-3 via the BBSome [93]. Co-immunoprecipitation experiments in vertebrate cells implicated IFT20 and IFT57 in binding kinesin-2 [45,102], and yeast two-hybrid analysis showed that IFT20 strongly interacts with both IFT57 and the KIF3B motor subunit of kinesin-2 [45]. However, these interactions were not verified in an independent study [5]. Tomographic reconstructions of *in situ* IFT particles revealed densities that are most likely kinesin motors connecting IFT particles to the axoneme, but the study did not identify which IFT proteins bind to the motors [32]. Live-cell fluorescence microscopy of IFT in *Chlamydomonas* has indicated that kinesin-2 (or at least the non-motor KAP subunit) may detach from IFT particles at the ciliary tip [103-105]. In contrast, kinesin-2 was observed to undergo retrograde transport in *C. elegans* [106]. If kinesin-2 does separate from IFT particles at the ciliary tip, this implies that kinesin-2 may ensure that only one type of motor is active at a time by inhibiting dynein 2 function during anterograde transport.

In *Chlamydomonas*, co-immunoprecipitation of IFT172 showed an interaction with cytoplasmic dynein 2 that was independent of IFT-A [107], and studies of temperature-sensitive mutants revealed that IFT172 is required for entry of dynein 2 into the flagellum [107,108]. Rescue of *Tetrahymena* IFT172 knockout cells with C-terminally truncated IFT172 constructs resulted in partial recovery of ciliary assembly and accumulation of IFT proteins at the ciliary tips, reminiscent of a retrograde IFT defect [109]. Thus, IFT172 may be divided into

an N-terminal PD that binds the IFT-B “core” and a C-terminal AD that interacts with dynein 2 (Figure 1). Additionally, co-immunoprecipitation of the microtubule plus-end-tracking protein EB1 from *Chlamydomonas* flagellar extract pulled down IFT172 independent of both IFT-A and IFT-B [110,111], although it is unknown which domain of IFT172 mediates this interaction. If binding EB1 modulates the affinity of IFT172 to either dynein 2 or the IFT-B “core”, this could contribute to the regulation of IFT turnaround at the ciliary tip. Interestingly, the partial depletion of dynein 2 from mutant *Chlamydomonas* flagella resulted in a compensatory increase in flagellar EB1 [112], so the two proteins may affect each other’s interaction with IFT172.

The BBSome: bridging IFT-A and IFT-B?

Purification of native IFT particles from *Chlamydomonas* flagella revealed that IFT-A and IFT-B complexes are loosely associated [2]. Despite their weak association *in vitro*, components of IFT-A and IFT-B move together in *C. elegans* sensory cilia, indicating that additional factors may play a role in the IFT complex stability *in vivo* [93,113]. Surprisingly, in *C. elegans bbs-7* and *bbs-8* mutants, the components of IFT-A and IFT-B are carried at different speeds by the heterotrimeric kinesin-2 and homodimeric OSM-3 motors, respectively [93]. This suggests that the BBSome, in addition to its well established function in cycling membrane proteins through cilia [82,84,114-117], may also play a role in holding IFT-A and IFT-B together *in vivo* [93]. This conclusion led to the proposal of the “mechanical competition” model, where the BBSome keeps the IFT-A and IFT-B complexes together resulting in IFT that proceeds at an intermediate speed [92]. However, two observations do not agree with the “mechanical competition” model. First, in *Chlamydomonas* flagella, the levels of BBS proteins are substoichiometric compared to IFT protein levels, and the BBSome component BBS4 undergoes IFT with only a subset of IFT particles [82]. Second, in *C. elegans*, a DYF-2 (IFT144 orthologue) point mutation resulted in the accumulation of BBSomes at the base of the cilium and the absence of BBSomes inside the cilium, but IFT-A and IFT-B complexes nevertheless moved together at intermediate speeds that were similar to wild-type [113]. Interestingly, in the *dyf-2* mutant, IFT-B components failed to associate with the retrograde IFT machinery and thus accumulated at the ciliary tip. These observations led to the proposal of a model where the BBSome plays a role in the formation of stable IFT complexes at the base and the tip of the cilium but is not necessary for IFT complex stability during anterograde IFT [113]. In any case, both models suggest that the BBSome interacts with components of both the IFT-A and IFT-B

complexes. Interestingly, in mice, BBSome component BBS1 was shown to directly interact with the IFT-A component WDR19 (IFT144 orthologue) [113]. As for the IFT-B complex, a large scale yeast two-hybrid study with *C. elegans* proteins revealed an interaction between the IFT-B accessory protein DYF-3 and the BBSome component BBS-7 [118]. Further studies are necessary to understand the regulatory role of the BBSome in IFT.

Conclusions

Although much is known about the overall architecture of the IFT complex and the role of IFT proteins in ciliary assembly and maintenance, molecular details concerning the distinctive roles of the 20 IFT proteins are still elusive. As pointed out in this review, it is likely that many IFT proteins possess principal domains required for IFT complex formation and auxiliary domains used to interact with ciliary cargo and motors. Functional dissection of these domains will remain the focus of extensive research in the coming years. While it is likely that highly abundant ciliary proteins such as tubulin, dynein arms and radial spokes have unique binding sites on the IFT complex, other ciliary cargo may compete via their CTS for binding to more generic cargo sites. In summary, the IFT complex contains numerous TPR and WD40 repeat domains that are expected to fulfill the task of selectively transporting a large number of ciliary proteins. Obtaining direct evidence for these interactions by means of either structural or functional studies would be a significant leap forward for the IFT field.

Abbreviations

5-HT₆R: serotonin receptor 6; AD: auxiliary domains; CTS: ciliary targeting sequence; GC: guanylyl cyclase; GPCR: G-protein coupled receptors; IFT: intraflagellar transport; NLS: nuclear localization signal; ODA: outer dynein arms; OS: outer segment; PC: polycystin; PD: principal domains; Shh: sonic hedgehog; SSTR3: somatostatin receptor 3; TPR: tetratricopeptide repeat; TRPV: Transient receptor potential vanilloid; TULP3: tubby like protein 3.

Competing interests

The authors declare that they have no competing interests.

Authors’ contributions

BDE wrote the “IFT complex-motor interactions” section. SB and EL wrote the rest of the manuscript. All the authors read and approved the final manuscript.

Acknowledgements

We thank Michael Taschner and three of the four anonymous reviewers for carefully reading and commenting on the manuscript. BDE was supported by a postdoctoral research fellowship granted by the Alexander von Humboldt Foundation.

Author details

¹Department of Structural Cell Biology, Max-Planck-Institute of Biochemistry, Am Klopferspitz 18, D-82152 Martinsried, Germany. ²Department of Molecular Structural Biology, Max-Planck-Institute of Biochemistry, Am Klopferspitz 18, D-82152 Martinsried, Germany.

Received: 9 April 2013 Accepted: 5 July 2013

Published: 14 Aug 2013

References

1. Kozminski KG, Johnson KA, Forscher P, Rosenbaum JL (1993) A motility in the eukaryotic flagellum unrelated to flagellar beating. *Proc Natl Acad Sci USA* 90:5519–5523
2. Cole DG, Diener DR, Himelblau AL, Beech PL, Fuster JC, Rosenbaum JL (1998) Chlamydomonas kinesin-II-dependent intraflagellar transport (IFT) particles contain proteins required for ciliary assembly in *Caenorhabditis elegans* sensory neurons. *J Cell Biol* 141:993–1008
3. Piperno G, Mead K (1997) Transport of a novel complex in the cytoplasmic matrix of *Chlamydomonas* flagella. *Proc Natl Acad Sci USA* 94:4457–4462
4. Pazour GJ, Baker SA, Deane JA, Cole DG, Dickert BL, Rosenbaum JL, Witman GB, Besharse JC (2002) The intraflagellar transport protein, IFT88, is essential for vertebrate photoreceptor assembly and maintenance. *J Cell Biol* 157:103–113
5. Follit JA, Xu F, Keady BT, Pazour GJ (2009) Characterization of mouse IFT complex B. *Cell Motil Cytoskeleton* 66:457–468
6. Blacque OE, Perens EA, Borojevich KA, Inglis PN, Li C, Warner A, Khattria J, Holt RA, Ou G, Mah AK, McKay SJ, Huang P, Swoboda P, Jones SJM, Marra MA, Baillie DL, Moerman DG, Shaham S, Leroux MR (2005) Functional genomics of the cilium, a sensory organelle. *Curr Biol* 15:935–941
7. Bacaj T, Lu Y, Shaham S (2008) The conserved proteins CHE-12 and DYF-11 are required for sensory cilium function in *Caenorhabditis elegans*. *Genetics* 178:989–1002
8. Fan ZC, Behal RH, Geimer S, Wang Z, Williamson SM, Zhang H, Cole DG, Qin H (2010) *Chlamydomonas* IFT70/CRDYF-1 is a core component of IFT particle complex B and is required for flagellar assembly. *Mol Biol Cell* 21:2696–2706
9. Kunitomo H, Iino Y (2008) *Caenorhabditis elegans* DYF-11, an orthologue of mammalian Traf3ip1/MIP-T3, is required for sensory cilia formation. *Genes Cells* 13:13–25
10. Wang Z, Fan Z-C, Williamson SM, Qin H (2009) Intraflagellar transport (IFT) protein IFT25 is a phosphoprotein component of IFT complex B and physically interacts with IFT27 in *Chlamydomonas*. *PLoS One* 4:e5384
11. Haycraft CJ, Schafer JC, Zhang Q, Taulman PD, Yoder BK (2003) Identification of CHE-13, a novel intraflagellar transport protein required for cilia formation. *Exp Cell Res* 284:249–261
12. Fliegauf M, Benzing T, Omran H (2007) When cilia go bad: cilia defects and ciliopathies. *Nat Rev Mol Cell Biol* 8:880–893
13. Davis EE, Zhang Q, Liu Q, Diplas BH, Davey LM, Hartley J, Stoetzel C, Szymanska K, Ramaswami G, Logan CV, Muzny DM, Young AC, Wheeler DA, Cruz P, Morgan M, Lewis LR, Cherukuri P, Maskeri B, Hansen NF, Mullikin JC, Blakesley RW, Bouffard GG, Gyapay G, Rieger S, Tönshoff B, Kern I, Soliman NA, Neuhaus TJ, Swoboda KJ, Kayserili H et al (2011) TTC21B contributes both causal and modifying alleles across the ciliopathy spectrum. *Nat Genet* 43:189–196
14. Arts HH, Bongers EMHF, Mans DA, van Beersum SEC, Oud MM, Bolat E, Spruijt L, Cornelissen EAM, Schuurs-Hoeijmakers JHM, de Leeuw N, Cormier-Daire V, Brunner HG, Knoers NVAM, Roepman R (2011) C14ORF179 encoding IFT43 is mutated in Sensenbrenner syndrome. *J Med Genet* 48:390–395
15. Walczak-Szulpa J, Eggenschwiler J, Osborn D, Brown DA, Emma F, Klingenberg C, Hennekam RC, Torre G, Garshasbi M, Tzschach A, Szczepanska M, Krawczynski M, Zachwieja J, Zwolinska D, Beales PL, Ropers H-H, Latos-Bielenska A, Kuss AW (2010) Cranioectodermal dysplasia, Sensenbrenner syndrome, is a ciliopathy caused by mutations in the IFT122 Gene. *Am J Hum Genet* 86:949–956
16. Cavalcanti DP, Huber C, Le Quan Sang KH, Baujat G, Collins F, Delezoide AL, Dagoneau N, Le Merrer M, Martinovic J, Mello MFS, Vekemans M, Munnich A, Cormier-Daire V (2011) Mutation in IFT80 in a fetus with the phenotype of Verma-Naumoff provides molecular evidence for Jeune-Verma-Naumoff dysplasia spectrum. *J Med Genet* 48:88–92
17. Perrault I, Saunier S, Hanein S, Filhol E, Bizet A, Collins F, Salih M, Silva E, Baudouin V, Oud M, Shannon N, Le Merrer M, Pietremont C, Beales P, Arts H, Munnich A, Kaplan J, Antignac C, Cormier Daire V, Rozet JM (2012) Mainzer-Saldino syndrome is a ciliopathy caused by mutations in the IFT140 gene. *Cilia* 1(Suppl 1):O28
18. Rosenbaum JL, Witman GB (2002) Intraflagellar transport. *Nat Rev Mol Cell Biol* 3:813–825
19. Beales PL, Bland E, Tobin JL, Bacchelli C, Tuysuz B, Hill J, Rix S, Pearson CG, Kai M, Hartley J (2007) IFT80, which encodes a conserved intraflagellar transport protein, is mutated in Jeune asphyxiating thoracic dystrophy. *Nat Genet* 39:727–729
20. Bredrup C, Saunier S, Oud MM, Fiskerstrand T, Hoischen A, Brackman D, Leh SM, Midtbø M, Filhol E, Bole-Feysot C, Nitschké P, Gilissen C, Haugen OH, Sanders J-SF, Stolte-Dijkstra I, Mans DA, Steenbergen EJ, Hamel BCJ, Matignon M, Pfundt R, Jeanpierre C, Boman H, Rødahl E, Veltman JA, Knappskog PM, Knoers NVAM, Roepman R, Arts HH (2011) Ciliopathies with skeletal anomalies and renal insufficiency due to mutations in the IFT-A gene WDR19. *Am J Hum Genet* 89:634–643
21. Gilissen C, Arts HH, Hoischen A, Spruijt L, Mans DA, Arts P, van Lier B, Steehouwer M, van Reeuwijk J, Kant SG, Roepman R, Knoers NVAM, Veltman JA, Brunner HG (2010) Exome sequencing identifies WDR35 variants involved in Sensenbrenner syndrome. *Am J Hum Genet* 87:418–423
22. Badano JL, Mitsuma N, Beales PL (2006) The Ciliopathies: an emerging class of human genetic disorders. *Annu Rev Genomics Hum Genet* 7:125–148
23. Ou G, Koga M, Blacque OE, Murayama T, Ohshima Y, Schafer JC, Li C, Yoder BK, Leroux MR, Scholey JM (2007) Sensory ciliogenesis in *Caenorhabditis elegans*: assignment of IFT components into distinct modules based on transport and phenotypic profiles. *Mol Biol Cell* 18:1554–1569
24. Hou Y, Qin H, Follit JA, Pazour GJ, Rosenbaum JL, Witman GB (2007) Functional analysis of an individual IFT protein: IFT46 is required for transport of outer dynein arms into flagella. *J Cell Biol* 176:653–665
25. Lucker BF, Miller MS, Dziedzic SA, Blackmarr PT, Cole DG (2010) Direct interactions of intraflagellar transport complex B proteins IFT88, IFT52, and IFT46. *J Biol Chem* 285:21508–21518
26. Richey EA, Qin H (2012) Dissecting the sequential assembly and localization of Intraflagellar transport particle complex B in *Chlamydomonas*. *PLoS One* 7:e43118
27. Kobayashi T, Gengyo-Ando K, Ishihara T, Katsura I, Mitani S (2007) IFT-81 and IFT-74 are required for intraflagellar transport in *C. elegans*. *Genes Cells* 12:593–602
28. Brazelton WJ, Amundsen CD, Silflow CD, Lefebvre PA (2001) The bld1 mutation identifies the *Chlamydomonas* OSM-6 homolog as a gene required for flagellar assembly. *Curr Biol* 11:1591–1594
29. Adhiambo C, Blisnick T, Toutirais G, Delannoy E, Bastin P (2009) A novel function for the atypical small G protein Rab-like 5 in the assembly of the trypanosome flagellum. *J Cell Sci* 122:834–841
30. Pazour G, Dickert BL, Vucica Y, Seeley ES, Rosenbaum JL, Witman GB, Cole DG (2000) *Chlamydomonas* IFT88 and its mouse homologue, polycystic kidney disease gene Tg737, are required for assembly of cilia and flagella. *J Cell Biol* 151:709–718
31. Tsujikawa M, Malicki J (2004) Intraflagellar transport genes are essential for differentiation and survival of vertebrate sensory neurons. *Neuron* 42:703–716
32. Pigino G, Geimer S, Lanzavecchia S, Paccagnini E, Cantele F, Diener DR, Rosenbaum JL, Lupetti P (2009) Electron-tomographic analysis of intraflagellar transport particle trains in situ. *J Cell Biol* 187:135–148
33. Bhogaraju S, Taschner M, Morawetz M, Basquin C, Lorentzen E (2011) Crystal structure of the intraflagellar transport complex 25/27. *EMBO J* 30:1907–1918
34. Lucker BF, Behal RH, Qin H, Siron LC, Taggart WD, Rosenbaum JL, Cole DG (2005) Characterization of the intraflagellar transport complex B core direct interaction of the IFT81 and IFT74/72 subunits. *J Biol Chem* 280:27688–27696
35. Taschner M, Bhogaraju S, Vetter M, Morawetz M, Lorentzen E (2011) Biochemical mapping of interactions within the intraflagellar transport (IFT) B core complex. *J Biol Chem* 286:26344–26352
36. Cole DG (2003) The intraflagellar transport machinery of *Chlamydomonas reinhardtii*. *Traffic* 4:435–442
37. Jékely G, Arendt D (2006) Evolution of intraflagellar transport from coated vesicles and autogenous origin of the eukaryotic cilium. *Bioessays* 28:191–198
38. van Dam TJP, Townsend MJ, Turk M, Schlessinger A, Sali A, Field MC, Huynen MA (2013) Evolution of modular intraflagellar transport from a coatomer-like progenitor. *Proc Natl Acad Sci USA* 110:6943–6948
39. Taschner M, Bhogaraju S, Lorentzen E (2012) Architecture and function of IFT complex proteins in ciliogenesis. *Differentiation* 83:512–522
40. Soding J, Biegert A, Lupas AN (2005) The HHpred interactive server for protein homology detection and structure prediction. *Nucleic Acids Res* 33(Web Server):W244–W248
41. Ahmed NT, Gao C, Lucker BF, Cole DG, Mitchell DR (2008) ODA16 aids axonemal outer row dynein assembly through an interaction with the intraflagellar transport machinery. *J Cell Biol* 183:313–322

42. Ahmed NT, Mitchell DR (2005) ODA16p, a Chlamydomonas flagellar protein needed for dynein assembly. *Mol Biol Cell* 16:5004–5012
43. Keady BT, Le YZ, Pazour GJ (2011) IFT20 is required for opsin trafficking and photoreceptor outer segment development. *Mol Biol Cell* 22:921–930
44. Omori Y, Zhao C, Saras A, Mukhopadhyay S, Kim W, Furukawa T, Sengupta P, Veraksa A, Malicki J (2008) Elipsa is an early determinant of ciliogenesis that links the IFT particle to membrane-associated small GTPase Rab8. *Nat Cell Biol* 10:437–444
45. Baker SA, Freeman K, Luby-Phelps K, Pazour GJ, Besharse JC (2003) IFT20 links Kinesin II with a mammalian intraflagellar transport complex that is conserved in motile flagella and sensory cilia. *J Biol Chem* 278:34211–34218
46. Keady BT, Samtani R, Tobita K, Tsuchiya M, San Agustin JT, Folliot JA, Jonassen JA, Subramanian R, Lo CW, Pazour GJ (2012) IFT25 links the signal-dependent movement of hedgehog components to intraflagellar transport. *Dev Cell* 22:940–951
47. Emanuelsson O (2002) Predicting protein subcellular localisation from amino acid sequence information. *Brief Bioinform* 3:361–376
48. Gilula NB, Satir P (1972) The ciliary necklace: a ciliary membrane specialization. *J Cell Biol* 53:494–509
49. Reiter JF, Blacque OE, Leroux MR (2012) The base of the cilium: roles for transition fibres and the transition zone in ciliary formation, maintenance and compartmentalization. *EMBO Rep* 13:608–618
50. Breslow DK, Nachury MV (2011) Primary cilia: how to keep the riff-raff in the plasma membrane. *Curr Biol* 21:R434–R436
51. Kee HL, Dishinger JF, Lynne Blasius T, Liu C-J, Margolis B, Verhey KJ (2012) A size-exclusion permeability barrier and nucleoporins characterize a ciliary pore complex that regulates transport into cilia. *Nat Cell Biol* 14:431–437
52. Francis SS, Sfakianos J, Lo B, Mellman I (2011) A hierarchy of signals regulates entry of membrane proteins into the ciliary membrane domain in epithelial cells. *J Cell Biol* 193:219–233
53. Geimer S, Melkonian M (2004) The ultrastructure of the Chlamydomonas reinhardtii basal apparatus: identification of an early marker of radial asymmetry inherent in the basal body. *J Cell Sci* 117:2663–2674
54. Craige B, Tsao C-C, Diener DR, Hou Y, Lechtreck K-F, Rosenbaum JL, Witman GB (2010) CEP290 tethers flagellar transition zone microtubules to the membrane and regulates flagellar protein content. *J Cell Biol* 190:927–940
55. Williams CL, Li C, Kida K, Inglis PN, Mohan S, Semenc L, Bialas NJ, Stupay RM, Chen N, Blacque OE, Yoder BK, Leroux MR (2011) MKS and NPHP modules cooperate to establish basal body/transition zone membrane associations and ciliary gate function during ciliogenesis. *J Cell Biol* 192:1023–1041
56. Hu Q, Milenkovic L, Jin H, Scott MP, Nachury MV, Spiliotis ET, Nelson WJ (2010) A septin diffusion barrier at the base of the primary cilium maintains ciliary membrane protein distribution. *Science* 329:436–439
57. Pazour GJ, Agrin N, Leszyk J, Witman GB (2005) Proteomic analysis of a eukaryotic cilium. *J Cell Biol* 170:103–113
58. Pazour GJ, Bloodgood RA (2008) Targeting proteins to the ciliary membrane. *Curr Top Dev Biol* 85:115–149
59. Dwyer ND, Adler CE, Crump JG, L'Etoile ND, Bargmann CI (2001) Polarized dendritic transport and the AP-1 μ 1 clathrin adaptor UNC-101 localize odorant receptors to olfactory cilia. *Neuron* 31:277–287
60. Corbit KC, Aanstad P, Singla V, Norman AR, Stainier D, Reiter JF (2005) Vertebrate Smoothed functions at the primary cilium. *Nature* 437:1018–1021
61. Palczewski K, Kumasaka T, Hori T, Behnke C, Motoshima H, Fox BA, Trong IL, Teller DC, Okada T, Stenkamp RE, Yamamoto M, Miyano M (2000) Crystal structure of rhodopsin: a G protein-coupled receptor. *Science* 289:733–734
62. Barbari NF, Johnson AD, Lewis JS, Askwith CC, Mykityn K (2008) Identification of ciliary localization sequences within the third intracellular loop of G protein-coupled receptors. *Mol Biol Cell* 19:1540–1547
63. Nagata A, Hamamoto A, Horikawa M, Yoshimura K, Takeda S, Saito Y (2013) Characterization of ciliary targeting sequence of rat melanin-concentrating hormone receptor 1. *Gen Comp Endocrinol* 188:159–165
64. Mukhopadhyay S, Wen X, Ratti N, Loktev A, Rangell L (2013) The ciliary G-protein-coupled receptor Gpr161 negatively regulates the sonic hedgehog pathway via cAMP signaling. *Cell* 152:210–223
65. Tam BM, Moritz OL, Hurd LB, Papermaster DS (2000) Identification of an outer segment targeting signal in the COOH terminus of rhodopsin using transgenic *Xenopus laevis*. *J Cell Biol* 151:1369–1380
66. Sung CH, Makino C, Baylor D, Nathans J (1994) A rhodopsin gene mutation responsible for autosomal dominant retinitis pigmentosa results in a protein that is defective in localization to the photoreceptor outer segment. *J Neurosci* 14:5818–5833
67. Geng L, Okuhara D, Yu Z, Tian X, Cai Y, Shibasaki S, Somlo S (2006) Polycystin-2 traffics to cilia independently of polycystin-1 by using an N-terminal RVxP motif. *J Cell Sci* 119:1383–1395
68. Ward HH, Brown-Glaberman U, Wang J, Morita Y, Alper SL, Bedrick EJ, Gattone VH, Deretic D, Wandering-Ness A (2011) A conserved signal and GTPase complex are required for the ciliary transport of polycystin-1. *Mol Biol Cell* 22:3289–3305
69. Hao L, Thein M, Brust-Mascher I, Civelekoglu-Scholey G, Lu Y, Acar S, Prevo B, Shaham S, Scholey JM (2011) Intraflagellar transport delivers tubulin isoforms to sensory cilium middle and distal segments. *Nat Cell Biol* 13:790–798
70. Scholey JM (2012) Kinesin-2 motors transport IFT-particles, dyneins and tubulin subunits to the tips of *Caenorhabditis elegans* sensory cilia: relevance to vision research? *Vision Res* 75:44–52
71. Dishinger JF, Kee HL, Jenkins PM, Fan S, Hurd TW, Hammond JW, Truong YN-T, Margolis B, Martens JR, Verhey KJ (2010) Ciliary entry of the kinesin-2 motor KIF17 is regulated by importin- β 2 and RanGTP. *Nat Cell Biol* 12:703–710
72. Fan S, Whiteman EL, Hurd TW, McIntyre JC, Dishinger JF, Liu CJ, Martens JR, Verhey KJ, Sajjan U, Margolis B (2011) Induction of Ran GTP drives ciliogenesis. *Mol Biol Cell* 22:4539–4548
73. Hurd TW, Fan S, Margolis BL (2011) Localization of retinitis pigmentosa 2 to cilia is regulated by Importin 2. *J Cell Sci* 124:718–726
74. Wolfrum U, Schmitt A (2000) Rhodopsin transport in the membrane of the connecting cilium of mammalian photoreceptor cells. *Cell Motil Cytoskeleton* 46:95–107
75. Trivedi D, Colin E, Louie CM, Williams DS (2012) Live-cell imaging evidence for the ciliary transport of Rod photoreceptor Opsin by Heterotrimeric Kinesin-2. *J Neurosci* 32:10587–10593
76. Marszalek JR, Liu X, Roberts EA, Chui D, Marth JD, Williams DS, Goldstein LSB (2000) Genetic evidence for selective transport of Opsin and Arrestin by Kinesin-II in mammalian photoreceptors. *Cell* 102:175–187
77. Qin H, Burnette DT, Bae Y-K, Forscher P, Barr MM, Rosenbaum JL (2005) Intraflagellar transport is required for the vectorial movement of TRPV channels in the ciliary membrane. *Curr Biol* 15:1695–1699
78. Huang K, Diener DR, Mitchell A, Pazour GJ, Witman GB, Rosenbaum JL (2007) Function and dynamics of PKD2 in Chlamydomonas reinhardtii flagella. *J Cell Biol* 179:501–514
79. Shih SM, Engel BD, Kocabas F, Bilyard T, Gennerich A, Marshall WF, Yildiz A (2013) Intraflagellar transport drives flagellar surface motility. *eLife* 2:e00744
80. Mukhopadhyay S, Wen X, Chih B, Nelson CD, Lane WS, Scales SJ, Jackson PK (2010) TULP3 bridges the IFT-A complex and membrane phosphoinositides to promote trafficking of G protein-coupled receptors into primary cilia. *Genes Dev* 24:2180–2193
81. Liem KF, Ashe A, He M, Satir P, Moran J, Beier D, Wicking C, Anderson KV (2012) The IFT-A complex regulates Shh signaling through cilia structure and membrane protein trafficking. *J Cell Biol* 197:789–800
82. Lechtreck K-F, Johnson EC, Sakai T, Cochran D, Ballif BA, Rush J, Pazour GJ, Ikebe M, Witman GB (2009) The Chlamydomonas reinhardtii BBSome is an IFT cargo required for export of specific signaling proteins from flagella. *J Cell Biol* 187:1117–1132
83. Jin H, White SR, Shida T, Schulz S, Aguiar M, Gygi SP, Bazan JF, Nachury MV (2010) The conserved Bardet-Biedl syndrome proteins assemble a coat that traffics membrane proteins to cilia. *Cell* 141:1208–1219
84. Barbari NF, Lewis JS, Bishop GA, Askwith CC, Mykityn K (2008) Bardet-Biedl syndrome proteins are required for the localization of G protein-coupled receptors to primary cilia. *Proc Natl Acad Sci USA* 105:4242–4246
85. Zhang Q, Seo S, Bugge K, Stone EM, Sheffield VC (2012) BBS proteins interact genetically with the IFT pathway to influence SHH-related phenotypes. *Hum Mol Genet* 21:1945–1953
86. Nachury MV, Loktev AV, Zhang Q, Westlake CJ, Peränen J, Merdes A, Slusarski DC, Scheller RH, Bazan JF, Sheffield VC, Jackson PK (2007) A core complex of BBS proteins cooperates with the GTPase Rab8 to promote ciliary membrane biogenesis. *Cell* 129:1201–1213
87. Blacque OE, Michael RJ, Chunmei L, Jonathan M, Leroux MR (2004) Loss of *C. elegans* BBS-7 and BBS-8 protein function results in cilia defects and compromised intraflagellar transport. *Genes Dev* 18:1630–1642
88. ter Haar E, Harrison SC, Kirchhausen T (2000) Peptide-in-groove interactions link target proteins to the β -propeller of clathrin. *Proc Natl Acad Sci USA* 97:1096–1100

89. Qin H, Diener DR, Geimer S, Cole DG, Rosenbaum JL (2004) Intraflagellar transport (IFT) cargo: IFT transports flagellar precursors to the tip and turnover products to the cell body. *J Cell Biol* 164:255–266
90. Bhowmick R, Li M, Sun J, Baker SA, Insinna C, Besharse JC (2009) Photoreceptor IFT complexes containing chaperones, guanylyl cyclase 1 and rhodopsin. *Traffic* 10:648–663
91. Snow JJ, Ou G, Gunnarson AL, Walker MRS, Zhou HM, Brust-Mascher I, Scholey JM (2004) Two anterograde intraflagellar transport motors cooperate to build sensory cilia on *C. elegans* neurons. *Nat Cell Biol* 6:1109–1113
92. Pan X, Ou G, Civelekoglu-Scholey G, Blacque OE, Endres NF, Tao L, Mogilner A, Leroux MR, Vale RD, Scholey JM (2006) Mechanism of transport of IFT particles in *C. elegans* cilia by the concerted action of kinesin-II and OSM-3 motors. *J Cell Biol* 174:1035–1045
93. Ou G, Blacque OE, Snow JJ, Leroux MR, Scholey JM (2005) Functional coordination of intraflagellar transport motors. *Nature* 436:583–587
94. Imanishi M, Endres NF, Gennerich A, Vale RD (2006) Autoinhibition regulates the motility of the *C. elegans* intraflagellar transport motor OSM-3. *J Cell Biol* 174:931–937
95. Pathak N, Obara T, Mangos S, Liu Y, Drummond IA (2007) The Zebrafish floor gene encodes an essential regulator of cilia tubulin polyglutamylation. *Mol Biol Cell* 18:4353–4364
96. Ikegami K, Heier RL, Taruishi M, Takagi H, Mukai M, Shimma S, Taira S, Hatanaka K, Morone N, Yao I, Campbell PK, Yuasa S, Janke C, MacGregor GR, Setou M (2007) Loss of tubulin polyglutamylation in ROSA22 mice is associated with abnormal targeting of KIF1A and modulated synaptic function. *Proc Natl Acad Sci USA* 104:3213–3218
97. Kubo T, Yanagisawa H-A, Yagi T, Hirono M, Kamiya R (2010) Tubulin polyglutamylation regulates axonemal motility by modulating activities of inner-arm dyneins. *Curr Biol* 20:441–445
98. Kubo T, Yagi T, Kamiya R (2012) Tubulin polyglutamylation regulates flagellar motility by controlling a specific inner-arm dynein that interacts with the dynein regulatory complex. *Cytoskeleton* 69:1059–1068
99. Santagata S, Boggon TJ, Baird CL, Gomez CA, Zhao J, SHan WS, Myszka DG, Shapiro L (2001) G-Protein signaling through tubby proteins. *Science* 292:2041–2050
100. Mukhopadhyay S, Jackson PK (2013) Cilia, tubby mice, and obesity. *Cilia* 2:1
101. Iomini C, Babaev-Khaimov V, Sassaroli M, Piperno G (2001) Protein particles in *Chlamydomonas* flagella undergo a transport cycle consisting of four phases. *J Cell Biol* 153:13–24
102. Krock BL, Perkins BD (2008) The intraflagellar transport protein IFT57 is required for cilia maintenance and regulates IFT-particle-kinesin-II dissociation in vertebrate photoreceptors. *J Cell Sci* 121:1907–1915
103. Engel BD, Ludington WB, Marshall WF (2009) Intraflagellar transport particle size scales inversely with flagellar length: revisiting the balance-point length control model. *J Cell Biol* 187:81–89
104. Engel BD, Lechtreck K-F, Sakai T, Ikebe M, Witman GB, Marshall WF (2009) Total internal reflection fluorescence (TIRF) microscopy of *chlamydomonas* flagella. *Methods Cell Biol* 93:157–177
105. Lechtreck KF (2013) In vivo imaging of IFT in *Chlamydomonas* flagella. *Methods Enzymol* 524:265–284
106. Signor D, Wedaman KP, Orozco JT, Dwyer ND, Bargmann CI, Rose LS, Scholey JM (1999) Role of a class DHC1b dynein in retrograde transport of IFT motors and IFT raft particles along cilia, but not dendrites, in chemosensory neurons of living *Caenorhabditis elegans*. *J Cell Biol* 147:519–530
107. Pedersen LB, Geimer S, Rosenbaum JL (2006) Dissecting the molecular mechanisms of intraflagellar transport in *chlamydomonas*. *Curr Biol* 16:450–459
108. Williamson SM, Silva DA, Richey E, Qin H (2012) Probing the role of IFT particle complex A and B in flagellar entry and exit of IFT-dynein in *Chlamydomonas*. *Protoplasma* 249:851–856
109. Tsao CC, Gorovsky MA (2008) Different effects of tetrahymena IFT172 domains on anterograde and retrograde intraflagellar transport. *Mol Biol Cell* 19:1450–1461
110. Pedersen LB, Miller MS, Geimer S, Jeffery LM, Rosenbaum JL, Cole DG (2005) *Chlamydomonas* IFT172 is encoded by FLA11, interacts with CrEB1, and regulates IFT at the flagellar tip. *Curr Biol* 15:262–266
111. Pedersen LB, Geimer S, Sloboda RD, Rosenbaum JL (2003) The microtubule plus end-tracking protein EB1 is localized to the flagellar tip and basal bodies in *Chlamydomonas reinhardtii*. *Curr Biol* 13:1969–1974
112. Engel BD, Ishikawa H, Wemmer KA, Geimer S, Wakabayashi K-I, Hirono M, Craige B, Pazour GJ, Witman GB, Kamiya R, Marshall WF (2012) The role of retrograde intraflagellar transport in flagellar assembly, maintenance, and function. *J Cell Biol* 199:151–167
113. Wei Q, Zhang Y, Li Y, Zhang Q, Ling K, Hu J (2012) The BBSome controls IFT assembly and turnaround in cilia. *Nat Cell Biol* 14:950–957
114. Lechtreck KF, Brown JM, Sampaio JL, Craft JM, Shevchenko A, Evans JE, Witman GB (2013) Cycling of the signaling protein phospholipase D through cilia requires the BBSome only for the export phase. *J Cell Biol* 201:249–261
115. Domire JS, Green JA, Lee KG, Johnson AD, Askwith CC, Mykytyn K (2010) Dopamine receptor 1 localizes to neuronal cilia in a dynamic process that requires the Bardet-Biedl syndrome proteins. *Cell Mol Life Sci* 68:2951–2960
116. Seo S, Zhang Q, Bugge K, Breslow DK, Searby CC, Nachury MV, Sheffield VC (2011) A novel protein LZTFL1 regulates ciliary trafficking of the BBSome and Smoothed. *PLoS Genet* 7:e1002358
117. Zhang Q, Nishimura D, Seo S, Vogel T, Morgan DA, Searby C, Bugge K, Stone EM, Rahmouni K, Sheffield VC (2011) Bardet-Biedl syndrome 3 (Bbs3) knockout mouse model reveals common BBS-associated phenotypes and Bbs3 unique phenotypes. *Proc Natl Acad Sci USA* 108:20678–20683
118. Li S, Armstrong CM, Bertin N, Ge H, Milstein S, Boxem M, Vidalain P-O, Han J-DJ, Chesneau A, Hao T, Goldberg DS, Li N, Martinez M, Rual J-F, Lamesch P, Xu L, Tewari M, Wong SL, Zhang LV, Berriz GF, Jacotot L, Vaglio P, Reboul J, Hirozane-Kishikawa T, Li Q, Gabel HW, Elewa A, Baumgartner B, Rose DJ, Yu H *et al* (2004) A map of the interactome network of the metazoan *C. elegans*. *Science* 303:540–543

10.1186/2046-2530-2-10

Cite this article as: Bhogaraju *et al*: Intraflagellar transport complex structure and cargo interactions. *Cilia* 2013, **2**:10

Submit your next manuscript to BioMed Central and take full advantage of:

- Convenient online submission
- Thorough peer review
- No space constraints or color figure charges
- Immediate publication on acceptance
- Inclusion in PubMed, CAS, Scopus and Google Scholar
- Research which is freely available for redistribution

Submit your manuscript at
www.biomedcentral.com/submit

