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The intraflagellar transport machinery in ciliary signaling

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Cilia and flagella on eukaryotic cells are slender microtubule-based projections surrounded by a membrane with a unique lipid and protein composition. It is now appreciated that cilia in addition to their established roles in motility also constitute hubs for cellular signaling by sensing external environmental cues necessary for organ development and maintenance of human health. Pathways reported to rely on the cilium organelle include Hedgehog, TGF-β, Wnt, PDGFRα, integrin and DNA damage repair signaling. An emerging theme in ciliary signaling is the requirement for active transport of signaling components into and out of the cilium proper. Here, we review the current state-of-the-art regarding the importance of intraflagellar transport and BBSome multi-subunit complexes in ciliary signaling.

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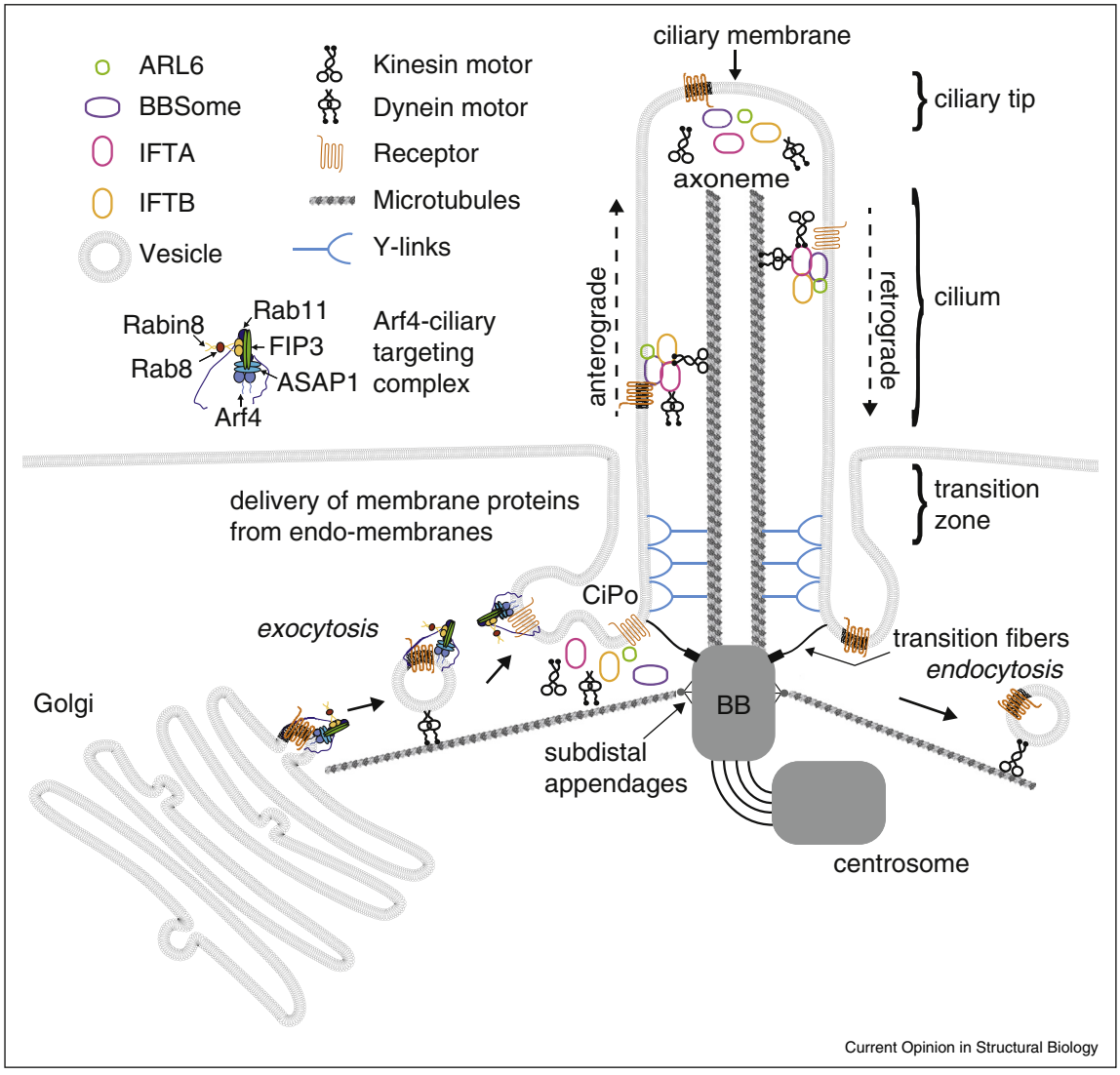
Introduction

Cilia are ancient evolutionarily conserved organelles that project from eukaryotic cells and are involved in cell motility, sensory reception and coordination of multiple signaling pathways (for a schematic of cilium architecture see Figure 1). The first observations of motile cilia on unicellular organisms (most likely protozoa) were made in 1675 by Antony van Leeuwenhoek, who described little animals, many times smaller than water-fleas, that moved themselves by putting forward two little horns (see English translations of Leeuwenhoek's letters to the Royal Society by C. Dobell [1]). More difficult to observe by light microscopy is the primary cilium that is non-motile, typically present in only one copy per cell and first described in the nineteenth century [2]. The first discovery of primary cilia on mammalian tissue is ascribed to the Swiss anatomist Karl W. Zimmermann who was also the first to suggest a sensory function for these organelles [3]. Although the potential sensory functions of the primary cilium were explored by some researchers in the 1980s and 1990s [4–6], this notion was largely ignored for most of the 20th century and the primary cilium was often referred to as rudimentary or abortive and regarded as a non-functional evolutionary remnant much like the human appendix [2]. This view was overturned at the beginning of the 21st century when polycystic kidney disease was coupled to primary cilia in the Oak Ridge Polycystic *Kidney* (orpk) mouse [7], and when genetic screens designed to discover novel factors in Hedgehog (Hh) signaling in the mouse uncovered a number of ciliary genes [8]. Shortly thereafter it was shown that proper Hh signaling requires the ciliary localization of key components in the Hh pathway, including the seven transmembrane class F G protein-coupled receptor (GPCR) Smoothened (Smo) as well as Gli transcription factors, and Suppressor of Fused (Sufu), which inhibit the transcriptional activity of Glis [9,10]. Indeed, it is now well-established that ciliary Hh signaling relies on the coordinated movement of multiple signaling components into and out of the cilium proper, including the Sonic hedgehog (Shh) receptor PTCH1, which when bound to its ligand exits the cilium in parallel with ciliary entry of Smo, thereby initiating a series of downstream events to activate Gli-mediated target gene expression [11].

Supporting the importance of the cilium in signaling is the finding that the coordination of a series of other pathways is integrated with the primary cilium, including those regulated by class A and B GPCRs [12,13], Receptor tyrosine kinases (RTKs) [14] and Transforming factor beta (TGF-β) receptors [15]. In addition, primary cilia have been shown to regulate Notch [16], Wingless/Int (Wnt) [17,18] and purinergic signaling [19], and the ciliary membrane in many cell types is enriched in receptors for extracellular matrix proteins [20,21] and ion channels of the TRP family, which may function in flow- and/or mechano-sensation [22]. Finally, DNA damage repair pathways also rely on the cilium for proper function [23,24].

It is not known why the cilium evolved as a nexus for signaling but some advantages may constitute: 1) the very large membrane-surface to volume ratio of the cilium allows for the possibility to organize and integrate diverse signaling pathways along the cilium-centrosome axis; 2) the increased activity of endo- and exocytosis at the ciliary pocket (CiPo) [25] at the base of the cilium that allows for

Figure 1



Schematics of a cilium with the ciliary axoneme, basal body (BB), membrane and transport complexes indicated. The basal body is anchored to the plasma membrane via transition fibers, and microtubules (MTs) spread out into the cytosol from the subdistal appendages of the basal body. In many cell types, the periciliary membrane (defined as the region between the ciliary transition zone (TZ) and the plasma membrane) is infolded to produce a ciliary pocket (CiPo). Transport of vesicles from the trans-Golgi network (TGN) or recycling endosomes to the cilium (exocytotic vesicles) and endocytotic vesicles emanating from periciliary membrane of the CiPo takes place along the cytosolic MTs using molecular motors that, depending on organism, differ from the IFT motors running along the ciliary axoneme. Ciliary targeting complexes assemble at the TGN to facilitate cargo-selection and vesicle budding and dynamically exchanges components along the trafficking pathway (drawn statically for simplicity). Signaling receptors, after delivery to the membrane at the ciliary base, are imported into the cilium proper either by IFT/BBSome-dependent or -independent mechanisms. After kinesin-mediated anterograde transport to the tip of the cilium, transport complexes are remodeled and transported back to the ciliary base in dynein-mediated retrograde transport. These ciliary transport processes are important for the import and export of several signaling receptors.

the spatiotemporal delivery and removal of ciliary membrane proteins via vesicular transport (Figure 1); and 3) the existence of an intraflagellar transport (IFT) system to efficiently move proteins between the base and tip of the cilium (Figure 2). Although different lines of evidence suggest that Hh signaling relies on the IFT machinery, it is not completely clear to what extent this also holds true for other ciliary signaling pathways. Ciliary signaling was comprehensively reviewed in several previously published contributions [11,14,26]. Here, we focus on the importance of multi-subunit transport complexes in the trafficking of ciliary signaling components.