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The essential roles of transition fibers in the context of cilia

Qing Wei[1,3], Kun Ling[3] and Jinghua Hu[1,2,3]

Once thought of as a vestigial organelle, the primary cilium is now recognized as a signaling hub for key cellular pathways in vertebrate development. The recent renaissance in cilia studies significantly improved our understanding of how cilia form and function, but little is known about how ciliogenesis is initiated and how ciliary proteins enter cilia. These important ciliary events require transition fibers (TFs) that are positioned at the ciliary base as symmetric nine-bladed propeller fibrous structures. Up until recently, TFs have been the most underappreciated ciliary structures due to limited knowledge about their molecular composition and function. Here, we highlight recent advances in our understanding of TF composition and the indispensable roles of TFs in regulating the initiation of ciliogenesis and the selective import of ciliary proteins.

Addresses
[1] Department of Nephrology and Hypertension, Mayo Clinic, Rochester, MN, USA
[2] Mayo Translational PKD Center, Rochester, MN, USA
[3] Department of Biochemistry and Molecular Biology, Mayo Clinic, Rochester, MN, USA

Corresponding author: Hu, Jinghua (hu.jinghua@mayo.edu)

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Introduction

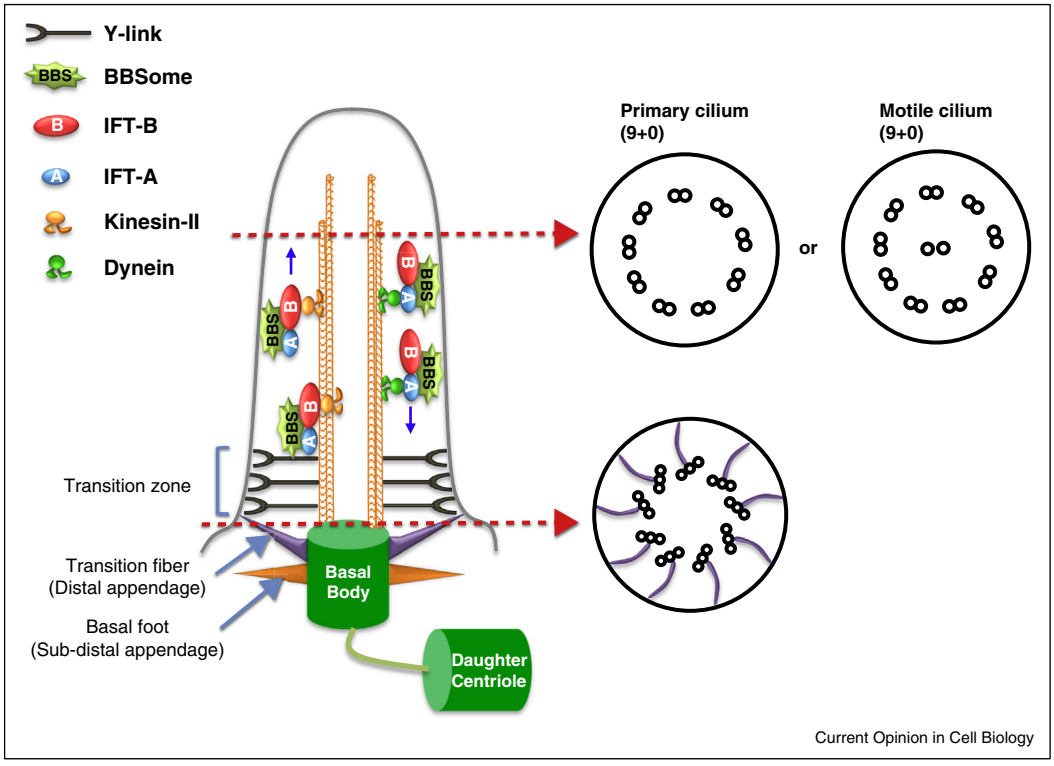
Microtubule-based cilia fulfill important sensory functions in most eukaryotic cells and are crucial in vertebrate embryonic development and tissue homeostasis [1,2]. Cilia dysfunction is correlated with an expanding spectrum of human genetic diseases (collectively termed ciliopathies) [3,4]. Since cilia are ubiquitous on cell surfaces, most ciliopathies occur as syndromic disorders that affect many vital organs during development, including the central nervous system (CNS), eyes, cardiovascular system, kidney, liver, limbs, bones, and fat storage tissue. Cilia dysfunction might affect as many as 100 human disorders [4,5]. Ciliopathies are probably the fastest growing category within human disease family: ~60 new causal loci were identified in last decade, and more are suspected [6].

Despite the physiological and clinical relevance of cilia, our understanding of how cilia form remains poor, and several key questions remain to be answered. For example, how is ciliogenesis initiated? At a morphological level, the mother centriole must dock to the membrane to initiate ciliogenesis. In different cell types, the mother centriole first attaches to vesicles, presumably Golgi-derived, in smooth muscle and endothelial cells [7••] or the cell membrane in some epithelial cells [8••,9]. Distal appendages (DAs), the fibrous structure at the distal end of the mother centriole, might mediate the centriole-membrane docking [10]. During the docking, the mother centriole transforms into the basal body, and its DAs mature into TFs. After that, the ciliary axoneme begins to elongate with the assistance of intraflagellar transport (IFT) machinery, which moves bidirectionally inside cilia to transport ciliary proteins essential for cilia formation, maintenance, and signaling [11–13].

As another question, how are cilia functionally separated from the cytosol? Unlike other membrane-enclosed cellular organelles, the cilium is open to the cytoplasm at its base. The ciliary base needs to control the selective entry of ciliary proteins and, thus, functionally separates the cilium from the cell body and makes it a discrete sensing organelle. The morphology of the ciliary base is highly conserved [14]: a basal body with fibrous apparatuses TFs and basal feet, and the transition zone (TZ, the proximal part of the axoneme that contains Y-links) (Figure 1). TFs form a 9-bladed propeller-like structure, and their anchoring points with the membrane define the border between the plasma membrane and the ciliary membrane [10]. Above the TFs, the Y-links of the TZ connect axonemal microtubules to the ciliary membrane [15]. The distinct locations of TFs and the TZ make them good candidates for the enigmatic ciliary gate or 'ciliary pore complex' that regulates the selective import of the ciliary proteins [13,14].

For many years, many roles were proposed for TFs in ciliogenesis initiation [10] and cilia import [13,16,17]. However, only recently, characterization of the molecular identities of DAs/TFs made it possible to elucidate and confirm the roles of TFs at a molecular level. Here, we review the insights that establish and expand our views of TFs as the indispensable structures in the context of cilia.

Figure 1



Schematic diagram of a cilium. All cilia have a microtubule-based core structure, called the axoneme, which projects from the basal body and is tightly surrounded by the ciliary membrane. Based on the motility, cilia can be divided into primary cilia (non-motile cilia) and motile cilia. The axoneme of primary cilia typically consists of nine microtubule doublets (9 + 0), typical motile cilia have an extra pair of microtubule singlet in the center of the ring of nine outer doublets (9 + 2). The basal body is transformed from the mother centriole during ciliogenesis. At the ciliary base, there are two structurally distinct sub-regions: TFs and the TZ. TFs are analogous to DAs of the mother centriole and form a 9-bladed propeller-like structure linking the basal body to the ciliary membrane. Basal feet (analogous to sub-DAs) locate below TFs on the basal body. Above TFs is the TZ that is characterized by the Y-links connecting axoneme microtubules to the ciliary membrane. Extension, maintenance and function of cilia require intraciliary transport machinery IFT, which is composed of IFT-A, IFT-B, BBSome and motors. IFT moves bidirectionally along the ciliary axoneme to transport cargos into or out of cilia. TFs, transition fibers; TZ, transition zone; DAs, distal appendages; IFT, intraflagellar transport; Sub-DAs, sub-distal appendages.

TF composition and assembly

So far, five proteins have been identified as genuine DA/TF components. These include CEP164, CEP83 (CCDC41), CEP89 (CCDC123), SCLT1 (sodium channel and clathrin linker 1) and FBF1 (Fas (TNFRSF6) binding factor 1) [18,19,20••,21••,22,23•]. CEP83 was reported to regulate the TF targeting of the other four proteins, and SCLT1 specifically affects the localization of CEP164 and FBF1 (Figure 2) [20••]. However, the strict role of CEP83 in regulating the TF localization of CEP164 has been questioned [23•]. Also Cby (Chibby) and TTBK2 (Tau tubulin kinase 2), two newly identified CEP164 interactors, localize to TFs and regulate ciliogenesis in different types of mammalian cells [24••,25••]. In super-resolution studies, the CEP164 ring is actually larger and more proximal than the Cby ring at the distal end of the mother centriole, suggesting that Cby attaches apically on TFs [24••].

The key structural TF components have not been determined due to the fact that the electron density of TFs in mammalian cells is too low for conclusive EM studies. TTBK2 and Cby are likely effectors of CEP164 that are recruited to TFs during ciliogenesis [24••,25••]. Since TFs exist in all ciliated organisms, the core structural component(s) should be evolutionarily conserved. However, of the other five components, only the homolog of FBF1 can be found in the genome of non-vertebrate ciliated organism *Caenorhabditis elegans* (Table 1), and depletion of DYF-19, the worm homolog of FBF1, does not affect TF biogenesis [21••]. These observations suggest that either some of the identified TF components are only mammalian-specific TF structural component(s), or more likely, the seven identified candidates are just the functional components of TFs, and the key structural components of TFs remain to be identified.

Several proteins have been implicated in the proper formation of DAs on mother centrioles. These include OFD1 (oral-facial-digital syndrome 1), C2CD3 (C2 calcium-dependent domain containing 3), ODF2 (outer dense