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Kinesin-2 Family Motors in the Unusual Photoreceptor Cilium

Jarema Malicki[1] and **Joseph C. Besharse**[2]

[1]MRC Centre for Developmental and Biomedical Genetics Department of Biomedical Science The University of Sheffield Firth Court, Western Bank Sheffield S10 2TN UK J.Malicki@sheffield.ac.uk tel: +44 (0)114 222-4638

[2]Department of Cell Biology, Neurobiology and Anatomy Medical College of Wisconsin 8701 Watertown, Plank Road Milwaukee, Wisconsin USA jbeshars@mcw.edu tel +1-414-305-1820

Abstract

This review focuses on recent advances in the understanding of kinesin-2 family motors in vertebrate photoreceptor development. Zebrafish photoreceptors develop by the 3rd day of embryogenesis, making it possible to study mutant phenotypes without the use of conditional alleles. Recent work using a zebrafish *kif3b* mutant allele validates the concept that the heterotrimeric kinesin II motor is generally required for ciliogenesis. In zebrafish photoreceptors, however, loss of *kif3b* function delays but does not block cilium formation. This is thought to occur because both *kif3b* or *kif3c* can dimerize with *kif3a* and function redundantly. The second ciliary kinesin thought to function in photoreceptor cells is *kif17*. Prior work has shown that either morpholino knockdown of this gene or the overexpression of its dominant negative form can reduce or delay photoreceptor cilium development without any evident impact on ciliogenesis in general. This has led to the idea that kif17 may play an important role only in some specialized cilium types, such the one in photoreceptor cells. In a recently identified *kif17* mutant, however, photoreceptor outer segments are formed by 5 dpf and an obvious delay of outer segment formation is seen only at the earliest stage analyzed (3 dpf). This work suggests that *kif17* plays a significant role mainly at an early stage of photoreceptor development. Taken together, these studies lead to an intriguing concept that as they differentiate photoreceptors alter their kinesin repertoire.

In vertebrate photoreceptors, the cilium is the photosensitive compartment of the cell. Photoreceptor cilia are exceptionally bulky and structurally complex compared to those in other cells (Fig. 1A). The most abundant protein component of the vertebrate photoreceptor cilium (traditionally referred to as “photoreceptor outer segment (OS) ”) is the visual pigment: rod opsin in rods and cone opsins in cones. It is estimated that ca. a billion opsin molecules are stored at any time in fully differentiated photoreceptor cilia (Pugh and Lamb, 2000). To accommodate such a huge quantity of the photopigment, the cone photoreceptor ciliary membrane is dramatically expanded and arranged into hundreds of parallel folds (Kennedy and Malicki, 2009). Similarly, rod photoreceptor cilia contain an extensive array of parallel membranes, which, in contrast to cones, form as stacks of flattened vesicles, and are referred to as discs. Thus both in rods and in cones, the cilium features a long stack of membranes oriented parallel to each other and perpendicular to the ciliary axis.

In addition to the visual pigment, structural proteins and the components of the phototransduction apparatus that function downstream of the photopigment are abundantly present in photoreceptor cilia. Similar to those in other cells, photoreceptor cilia lack the ability to synthesize proteins, and so all their protein components are transported from the cell body. This occurs throughout the lifetime of the cell, as the photoreceptor membrane is removed continuously from the distal portion of the cilium. In the mouse or rat rod photoreceptor, about 10% of membrane is eliminated daily via the phagocytic activity of retinal pigment epithelium from the distal portion of the cilium (LaVail, 1973). Data on opsin density in discs (Pugh and Lamb, 2000; Calvert, et al., 2001) and this level of turnover, which amounts to about 80 discs per day (about 2.3 μm of OS length), would require that roughly 100 rhodopsin molecules are transported into the outer segment every second or $8–9 \times 10^6$ per day. It should be emphasized that while such estimates are indicative of a high rate of transport, those values are based on the very small diameter of rodent discs. In other vertebrates, such as *Xenopus laevis* with comparable assembly rates but larger discs, the estimate for rhodopsin transported per day can be as much as 10 fold higher (Papermaster, et al., 1985).

Although bulky along most of its length, the photoreceptor cilium features a narrow constriction at its base. Cross-sections through this region reveal nine microtubule doublets arranged in a circle, and closely juxtaposed to the ciliary membrane. This segment of the photoreceptor cilium has been historically referred to as “the connecting cilium” (Fig. 1A). Electron microscopy of this region reveals that it contains Y-shaped elements linking ciliary microtubule doubles with the ciliary membrane (Besharse et al., 1985; Besharse and Horst, 1990). These structures, known as Y-links, are typical of the ciliary transition zone (Reiter et al., 2012). It is widely believed that all ciliary proteins are transported through this constriction into the more bulky distal part of the photoreceptor cilium.

The arrangement of microtubule doublets at the base of the photoreceptor cilium is typical of the majority of cilia, and suggests that transport mechanisms that operate in this region are also similar to those that function in most cilia. In contrast to other cells however, the sheer size of the photoreceptor cilium suggests that it may require atypical transport mechanisms to efficiently translocate all of its proteins, opsin in particular.

Numerous genetic studies have documented that the heterotrimeric kinesin-II, known to function in cilia of all organisms investigated so far, also plays a major role in vertebrate photoreceptors. As mutations in the kif3a and kif3b subunits of the heterotrimeric kinesin-II are lethal in the mouse, its function in vertebrate photoreceptors has to be studied using conditional alleles. The first study of this type used the IRBP promotor to drive the *cre* recombinase, and inactivate *kif3a* function in both rods and cones (Marszalek et al., 2000). It demonstrated that the loss of *kif3a* function results in the mislocalization of opsin and arrestin, but not transducin and peripherin. The changes in protein localization were followed by photoreceptor degeneration. A more in-depth analysis that followed nearly a decade later used different cre drives to eliminate *kif3a* function separately in rods and cones (Avasthi et al., 2009). Interestingly, this study revealed that *kif3a* functions somewhat differently in rods and cones. The excision of *kif3a* from cones resulted in the mistargeting of outer segment membrane proteins, including opsin, to the cell body. In contrast to that, this phenotype was substantially less pronounced in rod photoreceptors. Nonetheless, rods degenerated more rapidly, compared to cones in these mutants. Although this study clearly implicated *kif3a* in cone opsin transport, it raised questions about its role in the delivery of rod opsin into the rod outer segment. More recent studies support the concept that *kif3a* is required for both rod and cone opsin transport as well as for cell viability (Lopes et al., 2010; Trivedi et al., 2012).

The heterotrimeric kinesin-II consists of two motor subunits, encoded by the *kif3a* gene and either *kif3b* and *kif3c* loci (reviewed in Malicki, 2012). In addition, it contains an accessory non-motor subunit, encoded by *kap3*. Curiously, in contrast to mutations in *Kif3a* and *Kif3b*, knockout of *Kif3c* function in the mouse does not produce any obvious phenotype in photoreceptor cells (Jimeno et al., 2006). Further insights into the function of the heterotrimeric kinesin-II in photoreceptor cilia came from the studies of zebrafish mutant for the *kif3b* motor subunit (Zhao et al., 2012). In contrast to the mouse, and due to the absence of early embryonic lethality, the analysis of zebrafish photoreceptor defects in kinesin-II mutants does not require conditional mutant alleles. This simplifies the interpretation of mutant phenotypes as *kif3b* function is absent from the very outset of photoreceptor differentiation in zebrafish. Surprisingly, *kif3b* mutant cones differentiate cilia as well as relatively robust outer segments. The photoreceptor cilia are shorter, compared to the wild-type, but nonetheless their formation does not appear to require the *kif3b* function. This suggests that another gene functions redundantly with *kif3b* in zebrafish photoreceptors.

The *kif3b* and *kif3c* protein products are closely related, and both bind the *kif3a* protein but not each other (Muresan et al., 1998; Yang and Goldstein, 1998). These observations led to the idea that they may function redundantly as binding partners of the *kif3a* subunit. The *kif3c* protein expression data in photoreceptor cells argued, however, against such a possibility, perhaps delaying experimental tests of the redundancy hypothesis, which was proposed over a decade ago (Muresan et al., 1998; Yang and Goldstein, 1998). Nonetheless, when the redundancy was finally tested by morpholino knockdown of *kif3c* function in *kif3b* mutant zebrafish, it revealed that these two genes, indeed, function partially redundantly in photoreceptor cilia. This is not the case in the majority of other tissues, in which cilia do not form at all in the absence of *kif3b* function alone.

The study of the *kif3b* mutant zebrafish also revealed that cone outer segments form with a delay in this mutant background. This suggested that the *kif3c* kinesin function is not present at the very beginning of cilia formation in vertebrate photoreceptor cells, but, instead, becomes active at a later stage of differentiation. This possibility is supported by the results of *kif3c* overexpression, which induces earlier formation of cilia in *kif3b* mutant background (Zhao et al., 2012). Thus the photoreceptor cell is also unusual in that the repertoire of ciliary kinesins changes as the photoreceptor differentiates.

Although the heterotrimeric kinesin II motor is widely regarded as the canonical IFT kinesin in all cilia and flagella, homodimeric members of the kinesin-2 family (Osm-3, KIN5 and Kif17) have been implicated as ciliary kinesins in multiple systems, including photoreceptors. The earliest support for this accessory role was based on analysis of IFT in *C. elegans* in which dendritic processes of sensory neurons are ciliated and extend peripherally to perform their role as chemical and osmotic sensors (reviewed in (Inglis et al., 2007). In amphid channel cilia, kinesin II and homodimeric Osm-3 are present both in the dendritic and ciliary compartmen ts and are redundant in construction of the ciliary middle segment, which is composed of 9 doublet microtubules (Snow et al., 2004; Evans et al., 2006). In contrast, Osm-3 alone is necessary for forming the singlet extensions characteristic of the distal segment of these cilia. An important concept from the work in *C. elegans* is that the relative roles of kinesin II and Osm-3 may vary among different cilium types. For example, kinesin II and Osm-3 function completely redundantly to assemble the full length of amphid wing cilia (Evans et al., 2006), which lack distal singlets. Furthermore, analysis of yet another amphid cilium type (AWB) revealed that Osm-3 is not required for the formation of singlet microtubules in distal cilia and its movement in the middle segment is independent of kinesin II (Mukhopadhyay et al., 2007). In *C. elegans* the general conclusion is that both kinesin II and Osm-3 play a role in ciliogenesis and both operate as IFT kinesins. Kin5, a homodimeric kinesin homologous to Osm-3, has been proposed to play a role

similar to that in *C. elegans*, in the ciliate, *Tetrahymena thermophila* (Awan et al., 2004). Nonetheless, use of an alternative kinesin differs from the classic model for IFT based on *Chlamydomonas reinhartii* in which a homologue of Osm-3 has not been identified.

Among mammals the homologue of Osm-3, called Kif17, has been studied for more than a decade as a dendritic kinesin where it plays a non-ciliary role in trafficking of the NR2b subunit of NMDA receptors to dendritic spines (Setou et al., 2000; Yin et al., 2011). Kif17 has also been implicated in numerous other functions that include transport of other membrane channel subunits, translocation into the nucleus and dendritic trafficking of mRNA (Wong-Riley and Besharse, 2012). Despite these proposed non-ciliary functions, KIF17 is found in cilia including the axoneme of photoreceptors (Jenkins et al., 2006; Insinna et al., 2009; Dishinger et al., 2010) and current data suggest that as in *C. elegans* the role of Kif17 may vary among different types of vertebrate cilia. For example, Kif17 is expressed in olfactory cilia along with cyclic nucleotide gated (CNG) channels required for olfactory function. A role for Kif17 has been proposed based on exogenous expression of CNGBb1 in kidney epithelial cells that also express ciliary KIF17. In this system CNGBb1 is concentrated in the ciliary membrane and knockdown of Kif17 using a motor-less, dominant negative KIF17 construct ablates CNGB1b trafficking into cilia (Jenkins et al., 2006). Interestingly, dominant negative KIF17 had no effect on cilia length, suggesting that its role is in trafficking within the cilium rather than cilia morphogenesis. The latter finding is consistent with data from zebrafish showing that ciliogenesis in the pronephric kidney occurs normally in the presence of a *kif17*-targeted morpholino oligonucleotide sufficient to reduce *kif17* protein and to alter formation of photoreceptor outer segments (Insinna et al., 2008).

It has been proposed that *kif17* plays an important role in photoreceptor outer segment formation. This work was initiated based on parallels in the structure of photoreceptors and ciliated sensory dendrites in *C. elegans*, in which the axoneme is terminated with distal singlet microtubules. The data supporting this idea is based principally on morpholino knockdown of *kif17* in early zebrafish development (Insinna et al., 2008) and by over expression of a dominant negative *kif17* construct specifically in cone photoreceptors (Insinna et al., 2009). In each study, disruption of *kif17* impaired photoreceptor outer segment formation. The morpholino knockdown study was particularly notable in that outer segment formation was delayed with relatively little effect on overall development or ciliogenesis in other tissues, such as the pronephros, where cilia attained their normal structure and length. Likewise, dominant negative *kif17* expressed exclusively in zebrafish cones had effects mainly on outer segment formation in contrast to severe cell damage and cell death in cells expressing a dominant negative *kif3b*. As in the case of *C. elegans*, the morpholino and dominant negative interference with *kif17* function imply that this kinesin is not required for ciliogenesis in most cases but may play an important role in certain specialized ciliary types such as photoreceptors and olfactory cilia.

A different conclusion is supported by the studies of a *kif17* mutant line (*kif17*^{sa0119}), which has become available through the Sanger Welcome Trust TILLING project. It has been reported that kif17^{sa0119} fish develop normally, and, with the exception of a possible defect in olfactory ciliogenesis (Zhao et al., 2012) or the earliest stages of photoreceptor formation (Besharse laboratory, unpublished), ciliary defects are not detected. In contrast, both the *kif3b* mutant allele (Zhao et al., 2012) and morpholino knockdown of *kif3b* (Insinna et al., 2009) result in early embryonic phenotypes associated with wide failure of ciliogenesis. The extremely mild effects of *kif17*^{sa0119} suggest that *kif17* is largely dispensable for the morphogenesis of vertebrate cilia (Zhao et al., 2012).

Notably, *kif17*^{sa0119} mutant homozygotes do not display any obvious photoreceptor defects at 5 dpf or in adulthood. Even in the retinae of adult *kif17*^{sa0119} homozygotes, opsin localizes correctly, and no obvious cell loss is detected. These observations argue that *kif17* is unlikely to have a substantial contribution, directly or indirectly, to opsin transport in vertebrate photoreceptor cells. It remains possible, however, that the function of *kif17* in the vertebrate photoreceptor cell is transient. A temporal change in ciliary kinesin function has a precedent in aforementioned studies of *kif3c* (Zhao et al., 2012). *kif17* could function at early stages of outer segment formation and consequently its loss of function would affect outer segments at 3 but not at 5 dpf. Consistent with this, one of us has seen reduced outer segment formation in mutant fish at 3 dpf (Besharse laboratory, unpublished). Such a scenario would reconcile the results of morpholino knockdown with genetic analysis that relies on the use of the *kif17*^{sa0119} allele. Finally, one has to note that it also cannot be entirely excluded that *kif17*^{sa0119} is not a null allele (Besharse laboratory, unpublished), although published data demonstrate that it involves truncation of the C-terminal third of the kif17 polypeptide and a severe reduction in its mRNA expression level at 5 dpf (Zhao et al., 2012).

Studies of mutations in kinesin II proteins have provided a rather consistent story regarding the role of the heterotrimeric motor in photoreceptors of both fish and mice. However, the motor is likely to have multiple roles in addition to anterograde IFT (Tuma et al., 1998; Marszalek and Goldstein, 2000). While playing a role in outer segment IFT, kinesin II motors could also function in pre-synaptic trafficking and the formation of ribbon synapses (Insinna et al., 2009). Further work on this motor might logically focus on data implying that *kif3a* forms separate motors based on its association with either *kif3b* or *kif3c*. Although it appears that two such motors function redundantly in outer segment development, they could also regulate other trafficking events within the photoreceptor inner segment and the synaptic terminal. Kinesin function in photoreceptor differentiation may also be affected by tubulin modifications in axonemal microtubule doublets and, more distally, in singlets. This is another area that deserves investigation.

Additional work in both zebrafish and mice will be required to decipher the role of *kif17* in photoreceptors. As in zebrafish, *kif17* mutant mice do not display obvious ciliogenesis phenotypes (Yin et al., 2011) but do exhibit defects in trafficking within dendritic compartments. Further work on kif17 in photoreceptors will likely be guided by the finding that Kif17 associates with the IFT machinery and in at least in some cases accumulates in the distal domain of cilia (Dishinger et al., 2010). This suggests that unlike the kinesin II motor, Kif17 may not readily recycle through retrograde IFT. Its role in the distal domain remains unknown, but it could play a role in distal dynamics of the plus ends of singlet microtubules in the outer segment.

In summary, an interesting concept that has its origins in the studies of zebrafish photoreceptor cilia is that the repertoire of molecular motors changes as cilia differentiate differentiate (Fig. 1B). This appears to be the case for the heterotrimeric kinesin, as *kif3c* becomes active ca. 1–1.5 days after the onset of *kif3b* activity in photoreceptor outer segment formation (Zhao et al., 2012). Similarly, although this remains to be determined, *kif17* contribution may vary during photoreceptor differentiation (Fig. 1B). It remains to be seen whether such temporal variations in kinesin activity occur in cilia of other cells or are a peculiarity solely present in the unusual photoreceptor cilium.

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Highlights of this Review

- The assembly of large, bulky photoreceptor cilia may require special mechanisms.
- Photoreceptors have two heterotrimeric kinesin 2 motors with different subunits.
- Different heterotrimeric kinesins function sequentially in photoreceptor development.
- A third, homodimeric kinesin 2, *kif17*, is not globally required for ciliogenesis.
- *kif17* may be required in early photoreceptor cilium development.

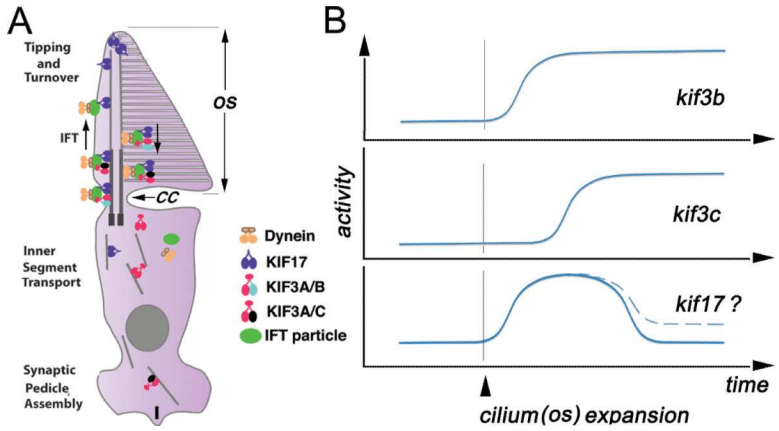

Fig. 1. Possible functions and temporal deployment of kinesin-2 motors during photoreceptor outer segment expansion

(A) Two hetrotrimeric motors based on *kif3b* and *kif3c* associated with *kif3a* and one homodimeric (*kif17*) motor are illustrated. Their possible roles in trafficking within the inner segment and synaptic pedicle or in IFT trafficking within the outer segment. In some cilia, kif17 uniquely accumulates at cilium distal tips in a phenomenon called tipping. (B) Plots illustrate that the onset of *kif3b* function occurs earlier than that of *kif3c*. Current data support a role for *Kif17* only during the early phase of cilium formation. This model is proposed primarily for cone photoreceptors. The function of *kif3c* in rods is less clear, as these cells die rapidly in zebrafish *kif3b* mutants. *OS*, outer segment; *CC*, connecting cilium, IFT, intraflagellar transport.