

# The effect of cytoplasmic dynein on the development and functional maintenance of retinal photoreceptor cells

B. JIA, C.-G. WANG, H. CHEN, X.-B. ZHOU, K. QIAN, C. CHEN,  
L.-X. XU, J.-L. FU

Department of Ophthalmology, The Second Hospital of Jilin University, Changchun City, China

**Abstract.** – Cytoplasmic dynein is a multi-subunit complex that includes cytoplasmic dynein-1 (dynein1) and cytoplasmic dynein-2 (dynein2). It participates in various basic cellular processes, including nuclear migration, mitotic spindle organization, chromosome separation during mitosis, and the location and function of numerous intracellular organelles. Retinal photoreceptor cells are terminally differentiated neurons that cannot regenerate and cannot be replaced once lost. It is thus crucial to study their development to facilitate the generation and improvement of photoreceptor disease treatments. The outer segment (OS) of photoreceptor cells is a specific sensory cilium. An increasing number of studies have shown that cytoplasmic dynein plays an essential role in the development of retinal photoreceptor cells. To date, people have done a lot of studies on the various functions of dynein in cells and have a very detailed understanding. However, the role of dynein in retinal photoreceptor cells has not been summarized in detail. This article summarizes the currently available knowledge relating to the effects and mechanisms of cytoplasmic dynein on the development and functional maintenance of retinal photoreceptor cells.

*Key Words:*

Cytoplasmic dynein, Retina, Photoreceptor cells, Material transport, Organelle location, Intraflagellar transport.

## Introduction

Photoreceptor cells are a kind of highly polarized cell in the retina, which are well known in the vertebrate nervous system and considered the best model with which to study neuron specialization and differentiation. Structurally, photoreceptor cells can be divided into three parts: outer segment, inner segment, and synapse.

During the apoptosis of photoreceptor cells retinal degeneration occurs, which results in visual impairment. As photoreceptor cells are the most vulnerable cells in the retina, it is imperative that we study their development to facilitate the generation and improvement of photoreceptor disease treatments.

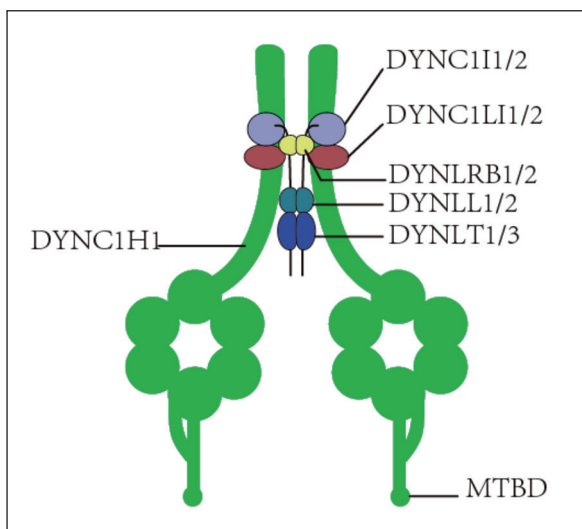
The outer segment (OS) of photoreceptor cells is a specific sensory cilium, which is connected to the inner segment (IS) by connecting cilia (CC). If the structure and function of the cilia are defective, it will lead to the reduction of material transport from the inner to the outer segments, which will lead to the shortening of outer segments and the dysfunction of photoreceptor cells, including ion movement and energy utilization in the light signal transmission and the phagocytosis of the retinal pigment epithelium (RPE) cells. In human retinal degenerative diseases, a large proportion of the mutant genes were found to be caused by the death of photoreceptor cells due to the influence of cilia transport.

Dynein is a protein complex in cilia that is involved in material transport between the synapse and soma of the neurons and is especially important for neuron function and survival. Dynein can be divided into two types: cytoplasmic dynein and axonemal dynein. Axonemal dynein only appears in the cilia and flagella, which transports goods from the axons to the cell bodies, while cytoplasmic dynein is responsible for the negative transport of all goods in the cells to the microtubules, including the transportation of organelles, proteins, mRNA, endosomes, and viruses. Cytoplasmic dynein can be divided into two types: dynein1 and dynein2. In this paper, we review the role of cytoplasmic dynein in the development and functional maintenance of photoreceptor cells.

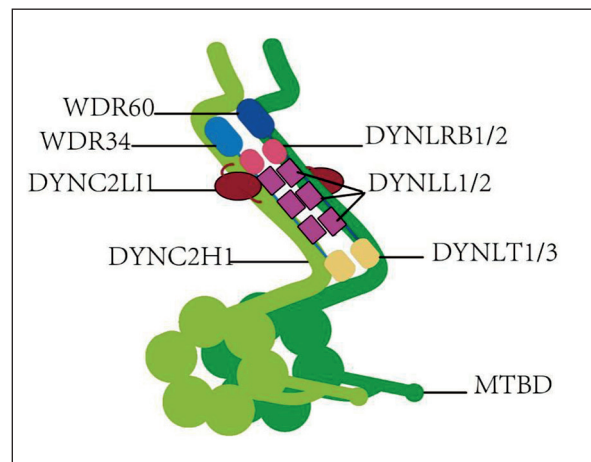
### The Structure and Function of Cytoplasmic Dynein

Cytoplasmic dynein is a type of multi-subunit complex that includes dynein1 and dynein2. Both of which contain four kinds of subunits, namely a dynein heavy chain (DHC), dynein intermediate chain (DIC), dynein light intermediate chain (DLIC), and dynein light chain (DLC). However, their specific compositions are slightly different. Dynein1 is composed of four different types of subunits: dynein1 heavy chain (DYNC1H1), dynein1 intermediate chain (DYNC1IC1/2), dynein1 light intermediate chain (DYNC1LI1/2) and three light chain families: roadblock (DYNLRB1/2), LC8 (DYNLL1/2), and Tctex (DYNLT1/3)<sup>1,2</sup> (Figure 1). Dynein2 is composed of five unique components: dynein2 heavy chain (DYNC2H1), dynein2 light intermediate chain (DYNC2LI1), dynein2 light chain (DYNC 2L1), and two different intermediate chains (WDR60 and WDR34), as well as the three light chains shared with Dynein1, roadblock, LC8, and TC-TEX<sup>3</sup> (Figure 2).

Dynein1 is related to a variety of cell functions under the action of dynein recruitment factors, such as the movement and positioning of nuclei, centrosomes, chromosomes, melanosome, and mitochondria; the positioning of the Golgi, endosome, and lysosome; the transportation of lipid droplets, mRNA, viruses, transcription



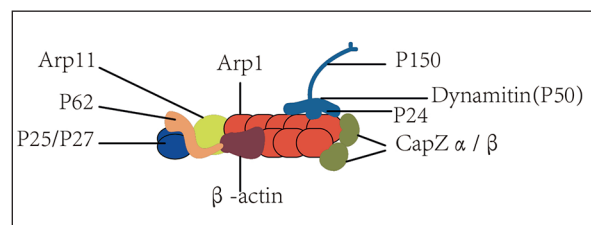
**Figure 1.** The structure of dynein1. Dynein1 is composed of four different types of subunits: dynein1 heavy chain (DYNC1H1), dynein1 intermediate chain (DYNC1IC1/2), dynein1 light intermediate chain (DYNC1LI1/2) and three light chain families: roadblock (DYNLRB1/2), LC8 (DYNLL1/2), and Tctex (DYNLT1/3).



**Figure 2.** The structure of dynein2. Dynein2 is composed of five unique components: dynein2 heavy chain (DYNC2H1), dynein2 light intermediate chain (DYNC2LI1), dynein2 light chain (DYNC 2L1), and two different intermediate chains (WDR60 and WDR34), as well as the three light chains shared with Dynein1, roadblock, LC8, and TC-TEX.

factors, centrosome components, and other cargoes; as well as retrograde axon transport in neurons<sup>4-10</sup>. Dynein1 can transport many cargoes along microtubules which have plus ends and minus ends<sup>2</sup>. The minus end of the microtubules originates from the microtubule organizing centers (MTOCs), while the plus end is usually located on the periphery of the cell<sup>2</sup>. Dynein2 is mainly involved in retrograde intraflagellar transport (IFT)<sup>11</sup> to establish and maintain the function of the cilia<sup>12</sup>.

In addition to the above two dynein complexes, there is also a multi-subunit protein complex, dynactin. Dynactin is a kind of dynein activator protein, which consists of 11 different subunits, namely dynactin1 (P150Glued), dynactin2 (p50 or dynamitin), dynactin3 (P24), dynactin4 (P62), and actin-related proteins Arp1 and Arp11 (ACTR10), as well as  $\beta$ -actin and CapZ $\alpha/\beta$ .



**Figure 3.** The structure of the dynactin complex. Dynactin consists of 11 different subunits, namely dynactin1 (P150Glued), dynactin2 (p50 or dynamitin), dynactin3 (P24), dynactin4 (P62), dynactin5 (P25), dynactin6 (P27), and actin-related proteins Arp1 and Arp11 (ACTR10), as well as  $\beta$ -actin and CapZ $\alpha/\beta$ .

dynactin5 (P25), dynactin6 (P27), and actin-related proteins Arp1 and Arp11 (ACTR10), as well as  $\beta$ -actin and CapZ $\alpha/\beta$ <sup>13</sup> (Figure 3). The core of dyactin consists of a 37-nanometer-long actin-like filament called the Arp1 rod<sup>14</sup>, consisting of eight identical Arp1 subunits, a  $\beta$ -actin molecule, capping proteins Cap $\alpha$  and Cap $\beta$ , and an Arp11 molecule. As the activator of dynein1 and the adaptor between dynein1 and the cargoes<sup>15-18</sup>, dynactin gives it additional functions by extending the scope of dynein1 for transporting cargoes and increasing the motor processability of dynein1<sup>19-21</sup>. For example, dynactin participates in the transportation and nuclear localization of dynein1<sup>10</sup>. Depending on the type of cargoes, dynein-dynactin uses different activating adaptor proteins including BICD2 and LIS1 to bind to the cargoes<sup>2,10</sup> (Figure 4). The activating adaptors connect with dynein by DLIC. Studies have shown that dynactin does not co-precipitate with dynein2<sup>22</sup>, and dynactin does not participate in the regulation of dynein2<sup>23</sup>.

#### ***Different Subtypes of Cytoplasmic Dynein in the Development and Functional Maintenance of Photoreceptor Cells***

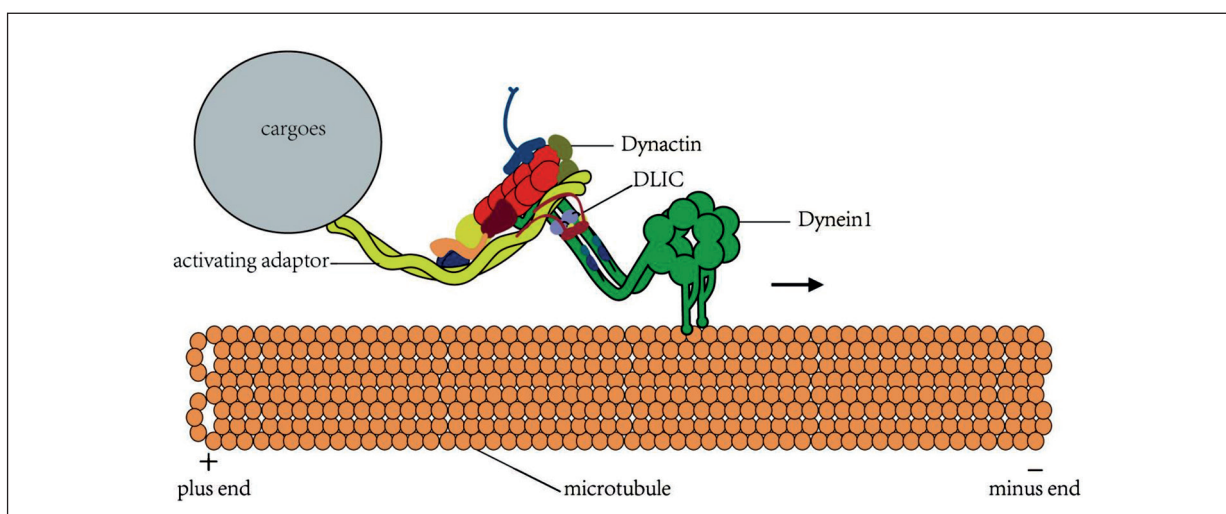
Dynein is required for different cellular processes and promotes the normal development and functional maintenance of photoreceptor cells<sup>21</sup>. In these cells it is specifically necessary for a variety of cellular processes, including organelle positioning, proper outer segment mor-

phology, nuclear movement and positioning, and potential Golgi vesicle transport<sup>4-10</sup>. In RPE cells, dynein1 participates in the movement of melanosomes along microtubules. In photoreceptor cells, dynein2 is an ATP-dependent motor protein, which is mainly associated with retrograde IFT for the establishment and functional maintenance of the cilia<sup>12</sup>. The dynactin complex is primarily responsible for assisting dynein1 to hold the position of the nucleus in the photoreceptor neurons after mitosis<sup>24</sup>. The dysfunction of dynein results in the abnormal structure and function of photoreceptor cells, which affects the development of the eyeball, leading to the occurrence of degenerative retinopathy.

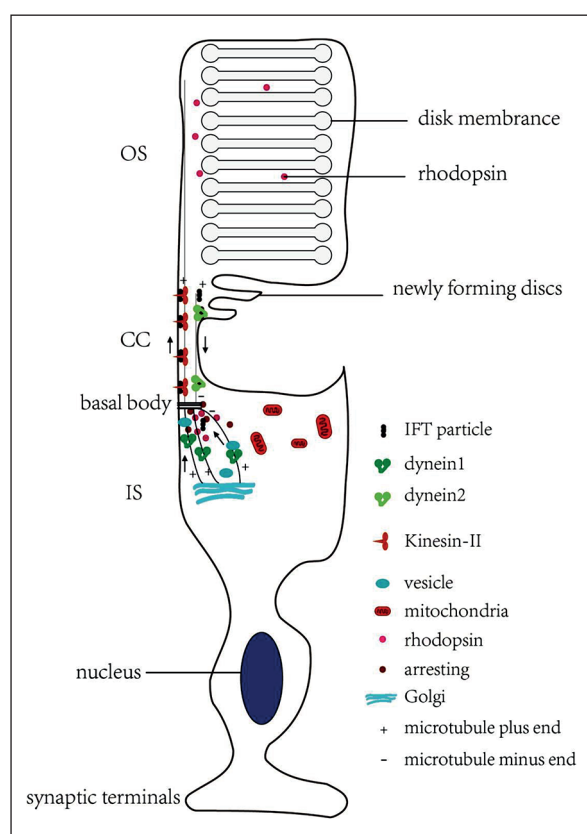
#### **Dynein1 in the Development and Functional Maintenance of Photoreceptor Cells**

##### ***Material Transport of Photoreceptor Cells and the Development of Outer Cilia***

Photoreceptor cells are highly polarized sensory neurons, which require large amounts of protein transport through narrow CCs to maintain the phototransduction of the photoreceptor OS (Figure 5). All proteins that are required for phototransduction are translated in the IS, and then transported to the OS through the CC<sup>25</sup>. Dynein is required in different cellular processes to promote the normal development, maintenance, and



**Figure 4.** Connection model for dynein1 and dynactin with cargoes. Dynein1-dynactin associates with cargoes using different activating adaptor proteins. The activating adaptors connect with dynein1 by the dynein light intermediate chains (DLIC). (IS: inner segment; CC: connecting cilium).



**Figure 5.** Dynein1 and dynein2 are required to transport cargoes in the outer segment (OS) of the photoreceptor cells. Cargoes required for OS such as rhodopsins and arrestins are transported by dynein1 to the basal body. Afterwards, the anterograde intraflagellar transport (IFT) mediated by kinesin-2 transports the cargoes needed for OS extension to the OS, then the IFT particles and kinesin-2 are transported back to basal body by dynein2 through retrograde IFT.

function of the photoreceptor cells<sup>26,27</sup>. Photoreceptor cell OS are a special kind of primary cilia composed of stacked disc membranes<sup>25</sup>. An essential aspect of OS maintenance is that they update approximately 10% of their length daily through a process called disc shedding. This process is supplemented by new external components to maintain the length of the OS, while IS produces the components required by the OS<sup>21</sup> (Figure 5). Rhodopsin is one of the main components of the disc membranes and plays an important role in the formation and maintenance of the OS<sup>28,29</sup>.

Dynein1 is considered to mediate the transport of substances in the photoreceptor cells, such as the transport of post-Golgi vesicles, especially those related to the transport of rhodopsin<sup>21</sup>. As the carboxy-terminal domain of rhodopsin can be combined with the dynein1 light chain

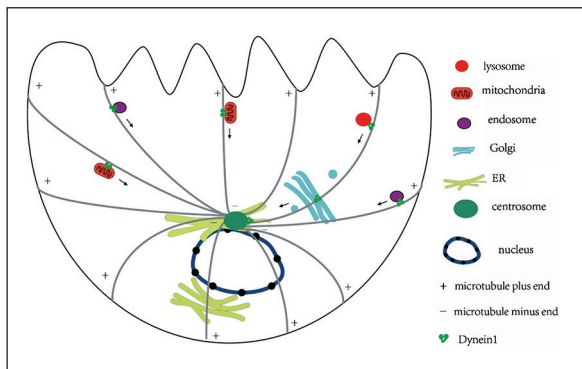
tctex-1, vesicles containing rhodopsin will be transported to microtubules by dynein1<sup>28</sup>. After which, all OS proteins such as rhodopsin with other components are transported to the base of the CC in a dynein1-dependent manner<sup>30-32</sup>, and finally delivered to the OS<sup>33</sup> (Figure 5). Kong et al<sup>34</sup> showed that the ablation of the *Dync11l* gene caused mouse rhodopsin and another OS protein, arrestin, to accumulate ectopically in the cell body and they could not be transported to the OS of the photoreceptor, leading to impaired OS growth and cilia development and triggering photoreceptor degeneration<sup>34</sup>. The overexpression of dynamitin, a component of dynactin, can block the transport from the endoplasmic reticulum to the Golgi<sup>7</sup>, indicating the role of dynein1 in the transport of substances from the endoplasmic reticulum to the Golgi.

Mutations in the *Dync1h1* gene lead to the zebrafish cannonball (CNB) phenotype, which is characterized by reduced eye size and photoreceptor cell defects, including discontinuities in the outer plexiform layer, shorter or missing OS, and the general destruction of organelle polarization in the IS. This shows that *DYNC1H1* plays a vital role in the development of zebrafish eyes<sup>21</sup>.

### **Organelle Localization of Photoreceptor Cells and the Movement of Melanosomes in RPE cells**

Dynein1 is involved in the localization of the Golgi, centrosome, mitochondria, and endoplasmic reticulum in retinal photoreceptor cells. Scholars<sup>35</sup> have been conducted to determine the relationship between dynein1 and the positioning of organelles. For example, the depletion of dynein1 prevents the in vitro movement of endosomes and lysosomes on microtubules, and heavy chain gene knockouts will cause the Golgi to break and disperse<sup>6</sup> (Figure 6).

In the photoreceptor cells of *DYNC11LII*<sup>-/-</sup> mice, the position of the endoplasmic reticulum is incorrect. The endoplasmic reticulum of the control group is only scattered in the IS and outer nuclear layer (ONL) of the retina, while the endoplasmic reticulum of the *DYNC11LII*<sup>-/-</sup> mice also exists in the outer plexiform layer (OPL)<sup>34</sup>. In another report, the mitochondria, centriole, and Golgi organelles were found to be mislocated in zebrafish CNB mutants<sup>21</sup>. Specifically, the mislocalization of mitochondria occurs in the IS. Numerous mitochondria were dispersed in the cytoplasm that lacked normal polarization,



**Figure 6.** Organelles that require dynein1 to assist in localization. The minus end of the microtubule originates from the microtubule organizing centers (MTOCs), the plus end is usually located on the periphery of the cell.

and isolated mitochondria can be seen beside the nucleus; the centrioles are also mislocated and separated from the basal body<sup>21</sup>. The location and organization of the Golgi apparatus in animal cells depends on the microtubules. Without the microtubules, the Golgi body becomes fragmented and gradually dispersed throughout the cell. Dynein1, which transports cargoes to the microtubule minus-end, is believed to be involved in the Golgi positioning process<sup>36</sup>. Abnormal Golgi localization and vesicle accumulation appeared in both the CNB phenotype and Dynact1h1 morpholino treated photoreceptor cells<sup>21</sup>.

In addition, studies<sup>37</sup> have shown that Dynein1 participates in the movement of melanosomes, which are organelles that absorb light, along the microtubules in RPE cells. They exist in the pigment cells of the skin and eyes, screening light to respond to changes in the outside conditions. In the eyes, the melanosomes change the visual sensitivity and resolution. In the RPE cells treated with DYNC1H1 shRNA, the distribution of the maximum melanosome velocity in the RPE of the retina changed. Compared with the control group, the frequency of the slow maximum speed was lower, and the frequency of the maximum speed was higher. The knockdown of DYNC1 reduced the proportion of active melanosomes from 30% to 10%. In addition, compared to the control group, melanosomes were mostly absent in the apical RPE<sup>37</sup>. This may reduce the ability of RPE cells to absorb light and protect themselves.

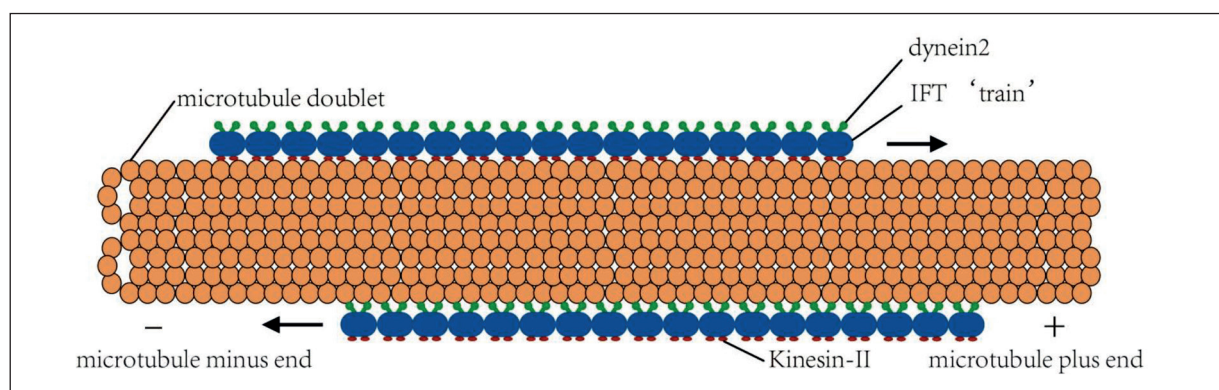
### **Retrograde IFT of Retinal Photoreceptor Cells**

IFT is the two-way transport of multi-subunit protein complexes (IFT particles) along the ax-

onomal microtubule doublets that involved anterograde IFT and retrograde IFT, which is vital for normal cilia assembly and functional maintenance<sup>38,39</sup>. IFT transports cargoes to the OS by CC<sup>40,41</sup>. Studies<sup>42-44</sup> on zebrafish mutants *ift57*, *ift88*, and *ift172* showed that IFT is a necessary process for the formation and maintenance of OS. IFT dysfunction can affect the health of OS, leading to photoreceptor cell death, inherited retinal disease (IRD), and even blindness<sup>40</sup>. In addition to the previously thought of anterograde IFT, retrograde IFT is also necessary for vertebrate IFT protein circulation and photoreceptor OS extension<sup>12</sup>.

In retinal photoreceptor cells, dynein2 is involved in the process of retrograde IFT. Different from anterograde IFT, the retrograde IFT motor is assembled by ATP-dependent homodimer dynein2 heavy chain DYNC2H1, light intermediate chain DYNC2LI1, intermediate chain DYNC2II1, and light chain LC8<sup>12</sup>. The photoreceptor OS of vertebrates is a sensory cilium that lacks the cellular mechanisms of protein synthesis. Therefore, the proteins required for phototransduction and the substances that constitute the OS, such as opsin, can only pass through the CC into the OS<sup>12</sup>. In addition to the phototransduction function, opsin plays an essential role in the structural maintenance of the OS. The functional establishment and survival of photoreceptor cells requires substances to be transported to the OS through the CC. Failure to efficiently transport opsin to the OS will result in photoreceptor degradation and death<sup>45,46</sup>. Dynein2, kinesin2, IFT-A complexes, and IFT-B complexes assemble to form IFT ‘trains’ (Figure 7). The process of moving cargoes to the cilia tip is mediated by kinesin2, but the IFT ‘trains’ return to the cell body is mediated by dynein2<sup>11</sup> (Figure 7). Throughout the process, dynein2 is passively transported from the base of the cilia to the tip of the cilia *via* kinesin2. After activation, dynein2 will actively transport IFT complexes and cargoes from the tip of the cilia to the basal body during retrograde IFT<sup>47,48</sup>.

The dysfunction of dynein2 will change the shape of the cilia, and the abnormalities can be observed in the mutants of some subunits. In zebrafish, compared to wild-type photoreceptors, the OS of many *DYNC2LII* variants of photoreceptor is composed of disordered membranes, some of which contain large vesicles. Vertically stacked membranes were observed in the OS of the *DYNC2LII* and *DYNC2II* variants<sup>12</sup>. These data indicate



**Figure 7.** Dynein2 is involved in the retrograde intraflagellar transport (IFT) process in photoreceptor cells. The IFT 'train' is assembled by dynein2, kinesin2, IFT-A complexes, and IFT-B complexes. When the IFT 'train' moves to the plus end of the microtubule doublets, it is mediated by kinesin-2, and when the IFT 'train' returns to the cell body, it is mediated by dynein2. In this way, the transportation of cargoes along the microtubule is completed.

that the standard extension of the OS requires retrograde IFT involving *DYNC2I1* and *DYNC2LI1*, suggesting that the circulation of the IFT protein may be a limiting factor for the growth of the OS. In addition, the mutation of *DYNC2H1* leads to the abnormal development of photoreceptors. Most of the cilia are missing in the *DYNC2H1* mutant, and the existing cilia are significantly shorter than the wild type cilia<sup>12</sup>. In the zebrafish variants injected with morpholino oligonucleotides targeting *DYNC2H1*, *DYNC2LI1*, and *DYNC2I1* genes, phenotypes like the *ift* mutants (such as *ift88* and *ift57*) appeared, which had small eyes and renal cysts. This suggests that the lack of function of these chains impairs retrograde IFT<sup>12</sup>.

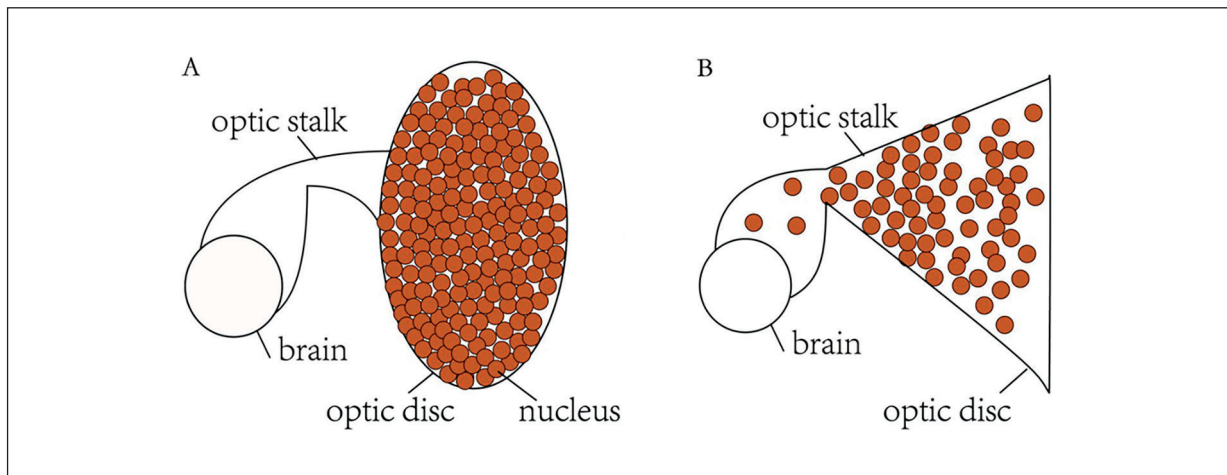
Zebrafish lacking dynein2 function have smaller eyes and relatively short photoreceptor OS, some of which are arranged in a disorderly manner, resulting in vesicle accumulation. The loss of dynein2 function leads to an evident decrease in the amplitude of the electroretinogram (ERG) a, b, and d waves, indicating that the loss of dynein2 reduces the photoreaction of photoreceptors<sup>12</sup>. Human exome sequencing and genome sequencing confirmed that the *DYNC2H1* variant is the cause of non-syndromic IRD<sup>49</sup>.

#### ***Dynactin Assists Dynein in the Nuclear Localization of Photoreceptor Cells***

Several studies<sup>50-52</sup> in different animals and cells have shown that the complex of dynein1 and dynactin plays an important role in maintaining the movement and positioning of the nucleus. Among them, dynactin participates in the transportation of dynein1 and the localization of the

nucleus, which is necessary for the maintenance of the nuclear position in drosophila photoreceptor neurons after mitosis<sup>24</sup>. Both the microtubule cytoskeleton and the actin cytoskeleton are involved in the localization of the nucleus in non-motor animal cells<sup>24,53</sup>. Dynactin plays a vital role in the organization of the microtubule cytoskeleton. The nucleus is usually related to the focus of the minus end of the microtubule. Scholars<sup>54</sup> in non-split cultured mammalian cells have shown that the cytoplasmic microtubule network and the minus end-oriented microtubule motor dynein are essential for maintaining the negative focus of the microtubule and the position of the nucleus. It has been determined<sup>52</sup> that mutations in the gene encoding P150glued will cause the photoreceptor nucleus to shift to the optic stalk and the brain, and the position of the photoreceptor nucleus depends on factors related to the microtubule cytoskeleton.

Whited et al<sup>24</sup> showed that dynactin is necessary for the correct positioning of the photoreceptor cell body and nucleus after mitosis, and kinesin can antagonize this function. The minus end-oriented motor dynein and dynactin co-localize to the photoreceptor cell nucleus, while the most end-oriented microtubule motor kinesin and dynactin have an antagonistic effect. The balance of their functions maintains the correct positioning of the photoreceptor nucleus<sup>24</sup>. Starr et al<sup>50</sup> proposed that kinesin1 is responsible for the advancement of the nucleus, while dynein mediates the short-term backward movement and rolling of the nucleus to solve the blockage of some cytoplasmic particles and ensure effective nuclear migration<sup>50</sup>.



**Figure 8.** Dynactin is necessary for the maintenance of the nuclear position in drosophila photoreceptor cells. A, The photoreceptor nuclei in wild-type drosophila were located on the top surface of the eye disc. B, In the *Glued1* mutant, the photoreceptor nuclei were randomly distributed throughout the eye disc and many nuclei migrated along the axon into the optic stalk or even into the brain.

The related role of the dynactin subunits has also been mentioned. Observations on zebrafish have indicated that nuclear localization requires P150<sup>55</sup>. In this report, zebrafish embryos carrying the P150 mutation (MOK mutant) failed to locate the photoreceptor nuclei correctly without affecting the morphogenesis of the entire cell<sup>55</sup>. When dynamitin is overexpressed, it shows the same phenotype as the MOK mutant<sup>55</sup>. Similar nuclear positioning errors also occur in the p150 mutant *Glued1* of *Drosophila*. In wild-type *Drosophila*, the photoreceptor nuclei were located on the top surface of the eye disc (Figure 8). However, in the *Glued1* mutant, the photoreceptor nuclei were randomly distributed throughout the eye disc, rarely occupying the normal apical area. Many cell nuclei migrated along the axon into the optic stalk<sup>52</sup> (Figure 8). After the photoreceptor axon extended to the target area in the brain, the interruption of dynactin function in the *Glued1* mutant caused the nuclei to leave the top of the neuron and move toward the brain, resulting in the photoreceptor having a “bipolar” morphology. At the same time, many photoreceptor cell bodies leave the top area of the eye disc and enter the optic stalk and brain<sup>24</sup>.

These results indicate that the nuclear localization of the photoreceptor cells is carried out through a dynein/dynactin-dependent pathway. Dynactin, dynein, and kinesin are all involved in the nuclear localization process of photoreceptors, but their specific mechanisms are currently unclear.

## Conclusions

The dynein complex is required to promote the development and functional maintenance of different cellular processes in the photoreceptor cells. Dynein1 is involved in the material transport of the photoreceptor cells, and the development of the outer cilia, organelle localization, and nuclear localization. Dynein2 is involved in the retrograde IFT of photoreceptor cells and is essential for the assembly and functional maintenance of the cilia. Dynactin gives dynein1 additional functions by extending the scope of its cargo transport and increasing its motor processability and then participates in its material transportation and nuclear localization. However, the current understanding of how dynein participates in the material transportation of the photoreceptor and the choice of cargoes, as well as the specific role played by each subunit and each chain is still limited and further research is required.

## Conflict of Interest

The Authors declare that they have no conflict of interests.

## Funding

The work was supported by the National Natural Science Foundation (81970836), the International Cooperation Project of Science and Technology Department of Jilin Province (20190701044GH), the Training Program for Outstanding Young Teachers of Jilin University (419080520313), and the

Natural Science Foundation Project of Science and Technology Department of Jilin Province (20200201360JC).

### Acknowledgements

We thank the reviewers of this article for their comments aimed at improving the quality of this manuscript.

### Authors' Contribution

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

## References

- 1) Pfister KK, Shah PR, Hummerich H, Russ A, Cotton J, Annuar AA, King SM, Fisher EMC. Genetic analysis of the cytoplasmic dynein subunit families. *PLoS Genet* 2006; 2: 11-26.
- 2) Reck-Peterson SL, Redwine WB, Vale RD, Carter AP. The cytoplasmic dynein transport machinery and its many cargoes. *Nat Rev Mol Cell Biol* 2018; 19: 382-398.
- 3) Toropova K, Zalyte R, Mukhopadhyay AG, Mladenov M, Carter AP, Roberts AJ. Structure of the dynein-2 complex and its assembly with intraflagellar transport trains. *Nat Struct Mol Biol* 2019; 26: 823-829.
- 4) Kon T, Nishiura M, Ohkura R, Toyoshima YY, Sutoh K. Distinct functions of nucleotide-binding/hydrolysis sites in the four AAA modules of cytoplasmic dynein. *Biochemistry* 2004; 43: 11266-11274.
- 5) Ilangovan U, Ding W, Zhong Y, Wilson CL, Groppe JC, Trbovich JT, Zuniga J, Demeler B, Tang Q, Gao GF, Mulder KM, Hinck AP. Structure and dynamics of the homodimeric dynein light chain km23. *J Mol Biol* 2005; 352: 338-354.
- 6) Harada A, Takei Y, Kanai Y, Tanaka Y, Nonaka S, Hirokawa N. Golgi vesiculation and lysosome dispersion in cells lacking cytoplasmic dynein. *J Cell Biol* 1998; 141: 51-59.
- 7) Burkhardt JK, Echeverri CJ, Nilsson T, Vallee RB. Overexpression of the dynamitin (p50) subunit of the dynactin complex disrupts dynein-dependent maintenance of membrane organelle distribution. *J Cell Biol* 1997; 139: 469-484.
- 8) Vaughan PS, Leszyk JD, Vaughan KT. Cytoplasmic dynein intermediate chain phosphorylation regulates binding to dynactin. *J Biol Chem* 2001; 276: 26171-26179.
- 9) King SJ, Brown CL, Maier KC, Quintyne NJ, Schroer TA. Analysis of the dynein-dynactin interaction in vitro and in vivo. *Mol Biol Cell* 2003; 14: 5089-5097.
- 10) Tsai J-W, Bremner KH, Vallee RB. Dual subcellular roles for LIS1 and dynein in radial neuronal migration in live brain tissue. *Nat Neurosci* 2007; 10: 970-979.
- 11) Vuolo L, Stevenson NL, Mukhopadhyay AG, Roberts AJ, Stephens DJ. Cytoplasmic dynein-2 at a glance. *J Cell Sci* 2020; 133.
- 12) Krock BL, Mills-Henry I, Perkins BD. Retrograde Intraflagellar Transport by Cytoplasmic Dynein-2 Is Required for Outer Segment Extension in Vertebrate Photoreceptors but Not Arrestin Translocation. *Invest Ophthalmol Vis Sci* 2009; 50: 5463-5471.
- 13) Hammesfahr B, Kollmar M. Evolution of the eukaryotic dynactin complex, the activator of cytoplasmic dynein. *BMC Evol Biol* 2012; 12.
- 14) Schroer TA. Dynactin. *Annu Rev Cell Dev Biol* 2004; 20: 759-779.
- 15) Gill SR, Schroer TA, Szilak I, Steuer ER, Sheetz MP, Cleveland DW. Dynactin, a conserved, ubiquitously expressed component of an activator of vesicle motility mediated by cytoplasmic dynein. *J Cell Biol* 1991; 115: 1639-1650.
- 16) Holleran EA, Tokito MK, Karki S, Holzbaur EL. Centractin (ARP1) associates with spectrin revealing a potential mechanism to link dynactin to intracellular organelles. *J Cell Biol* 1996; 135: 1815-1829.
- 17) Muresan V, Stankewich MC, Steffen W, Morrow JS, Holzbaur ELF, Schnapp BJ. Dynactin-dependent, dynein-driven vesicle transport in the absence of membrane proteins: A role for spectrin and acidic phospholipids. *Mol Cell* 2001; 7: 173-183.
- 18) Carter AP, Diamant AG, Urnavicius L. How dynein and dynactin transport cargos: a structural perspective. *Curr Opin Struct Biol* 2016; 37: 62-70.
- 19) Vallee RB, Williams JC, Varma D, Barnhart LE. Dynein: An ancient motor protein involved in multiple modes of transport. *J Neurobiol* 2004; 58: 189-200.
- 20) Hirokawa N. Kinesin and dynein superfamily proteins and the mechanism of organelle transport. *Science* 1998; 279: 519-526.
- 21) Insinna C, Baye LM, Amsterdam A, Besharse JC, Link BA. Analysis of a zebrafish *dync1h1* mutant reveals multiple functions for cytoplasmic dynein 1 during retinal photoreceptor development. *Neural Dev* 2010; 5: 12.
- 22) Asante D, Stevenson NL, Stephens DJ. Subunit composition of the human cytoplasmic dynein-2 complex. *J Cell Sci* 2014; 127: 4774-4787.
- 23) Roberts AJ. Emerging mechanisms of dynein transport in the cytoplasm versus the cilium. *Biochem Soc Trans* 2018; 46: 967-982.
- 24) Whited JL, Cassell A, Brouillette M, Garrity PA. Dynactin is required to maintain nuclear position within postmitotic *Drosophila* photoreceptor neurons. *Development* 2004; 131: 4677-4686.
- 25) Ramamurthy V, Cayouette M. Development and disease of the photoreceptor cilium. *Clin Genet* 2009; 76: 137-145.
- 26) Insinna C, Besharse JC. Intraflagellar transport and the sensory outer segment of vertebrate photoreceptors. *Dev Dyn* 2008; 237: 1982-1992.
- 27) Kennedy B, Malicki J. What Drives Cell Morphogenesis: A Look Inside the Vertebrate Photoreceptor. *Dev Dyn* 2009; 238: 2115-2138.

- 28) Kwok MCM, Holopainen JM, Molday LL, Foster LJ, Molday RS. Proteomics of photoreceptor outer segments identifies a subset of SNARE and Rab proteins implicated in membrane vesicle trafficking and fusion. *Mol Cell Proteomics* 2008; 7: 1053-1066.
- 29) Harosi FI. Absorption spectra and linear dichroism of some amphibian photoreceptors. *J Gen Physiol* 1975; 66: 357-382.
- 30) Tai AW, Chuang JZ, Bode C, Wolfrum U, Sung CH. Rhodopsin's carboxy-terminal cytoplasmic tail acts as a membrane receptor for cytoplasmic dynein by binding to the dynein light chain Tc-tex-1. *Cell* 1999; 97: 877-887.
- 31) Papermaster DS, Schneider BG, Besharse JC. Vesicular transport of newly synthesized opsin from the Golgi apparatus toward the rod outer segment. Ultrastructural immunocytochemical and autoradiographic evidence in *Xenopus* retinas. *Invest Ophthalmol Vis Sci* 1985; 26: 1386-1404.
- 32) Papermaster DS, Schneider BG, DeFoe D, Besharse JC. Biosynthesis and vectorial transport of opsin on vesicles in retinal rod photoreceptors. *J Histochem Cytochem* 1986; 34: 5-16.
- 33) Wolfrum U, Schmitt A. Rhodopsin transport in the membrane of the connecting cilium of mammalian photoreceptor cells. *Cell Motil Cytoskeleton* 2000; 46: 95-107.
- 34) Kong S, Du X, Peng C, Wu Y, Li H, Jin X, Hou L, Deng K, Xu T, Tao W. *Dlic1* deficiency impairs ciliogenesis of photoreceptors by destabilizing dynein. *Cell Res* 2013; 23: 835-850.
- 35) Blocker A, Severin FF, Burkhardt JK, Bingham JB, Yu H, Olivo JC, Schroer TA, Hyman AA, Griffiths G. Molecular requirements for bi-directional movement of phagosomes along microtubules. *J Cell Biol* 1997; 137: 113-129.
- 36) Allan VJ, Thompson HM, McNiven MA. Motoring around the Golgi. *Nat Cell Biol* 2002; 4: E236-E242.
- 37) Jiang M, Paniagua AE, Volland S, Wang H, Balaji A, Li DG, Lopes VS, Burgess BL, Williams DS. Microtubule motor transport in the delivery of melanosomes to the actin-rich apical domain of the retinal pigment epithelium. *J Cell Sci* 2020; 133.
- 38) Ocbina PJR, Anderson KV. Intraflagellar Transport, cilia, and mammalian Hedgehog signaling: analysis in mouse embryonic fibroblasts. *Dev Dyn* 2008; 237: 2030-2038.
- 39) Yi P, Li W-J, Dong M-Q, Ou G. Dynein-Driven Retrograde Intraflagellar Transport Is Triphasic in *C. elegans* Sensory Cilia. *Curr Biol* 2017; 27: 1448-1461.e7.
- 40) Pazour GJ, Baker SA, Deane JA, Cole DG, Dickert BL, Rosenbaum JL, Witman GB, Besharse JC. The intraflagellar transport protein, IFT88, is essential for vertebrate photoreceptor assembly and maintenance. *J Cell Biol* 2002; 157: 103-113.
- 41) Marszalek JR, Liu XR, Roberts EA, Chui D, Marth JD, Williams DS, Goldstein LSB. Genetic evidence for selective transport of opsin and arrestin by kinesin-II in mammalian photoreceptors. *Cell* 2000; 102: 175-187.
- 42) Sukumaran S, Perkins BD. Early defects in photoreceptor outer segment morphogenesis in zebrafish *ift57*, *ift88* and *ift172* Intraflagellar Transport mutants. *Vision Res* 2009; 49: 479-489.
- 43) Krock BL, Perkins BD. The intraflagellar transport protein IFT57 is required for cilia maintenance and regulates IFT-particle-kinesin-II dissociation in vertebrate photoreceptors. *J Cell Sci* 2008; 121: 1907-1915.
- 44) Tsujikawa M, Malicki J. Intraflagellar transport genes are essential for differentiation and survival of vertebrate sensory neurons. *Neuron* 2004; 42: 703-716.
- 45) Grimm C, Wenzel A, Hafezi F, Yu S, Redmond TM, Reme CE. Protection of *Rpe65*-deficient mice identifies rhodopsin as a mediator of light-induced retinal degeneration. *Nat Genet* 2000; 25: 63-66.
- 46) Portera-Cailliau C, Sung CH, Nathans J, Adler R. Apoptotic photoreceptor cell death in mouse models of retinitis pigmentosa. *Proc Natl Acad Sci U S A* 1994; 91: 974-978.
- 47) Hao L, Efimenko E, Swoboda P, Scholey JM. The retrograde IFT machinery of *C. elegans* cilia: two IFT dynein complexes? *PLoS One* 2011; 6: e20995.
- 48) Rosenbaum JL, Witman GB. Intraflagellar transport. *Nat Rev Mol Cell Biol* 2002; 3: 813-825.
- 49) Vig A, Poulter JA, Ottaviani D, Tavares E, Toropova K, Tracewska AM, Mollica A, Kang J, Kehelwathugoda O, Paton T, Maynes JT, Wheway G, Arno G, Khan KN, McKibbin M, Toomes C, Ali M, Di Scipio M, Li S, Ellingford J, Black G, Webster A, Rydzanicz M, Stawinski P, Ploski R, Vincent A, Cheetham ME, Inglehearn CF, Roberts A, Heon E, Genom England Res C. *DYNC2H1* hypomorphic or retina-predominant variants cause non-syndromic retinal degeneration. *Genet Med* 2020; 22: 2041-2051.
- 50) Starr DA. Watching nuclei move: Insights into how kinesin-1 and dynein function together. *Bioarchitecture* 2011; 1: 9-13.
- 51) Swan A, Nguyen T, Suter B. *Drosophila* Lissencephaly-1 functions with Bic-D and dynein in oocyte determination and nuclear positioning. *Nat Cell Biol* 1999; 1: 444-449.
- 52) Fan SS, Ready DF. Glued participates in distinct microtubule-based activities in *Drosophila* eye development. *Development* 1997; 124: 1497-1507.
- 53) Starr DA, Han M. ANChors away: an actin based mechanism of nuclear positioning. *J Cell Sci* 2003; 116: 211-216.
- 54) Quinyne NJ, Gill SR, Eckley DM, Crego CL, Compton DA, Schroer TA. Dynactin is required for microtubule anchoring at centrosomes. *J Cell Biol* 1999; 147: 321-334.
- 55) Tsujikawa M, Omori Y, Biyanwila J, Malicki J. Mechanism of positioning the cell nucleus in vertebrate photoreceptors. *Proc Natl Acad Sci U S A* 2007; 104: 14819-14824.