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CELL SCIENCE AT A GLANCE

Photoreceptors at a glance

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ABSTRACT

Retinal photoreceptor cells contain a specialized outer segment (OS) compartment that functions in the capture of light and its conversion into electrical signals in a process known as phototransduction. In rods, photoisomerization of 11-*cis* to all-*trans* retinal within rhodopsin triggers a biochemical cascade culminating in the closure of cGMP-gated channels and hyperpolarization of the cell. Biochemical reactions return the cell to its 'dark state' and the visual cycle converts all-*trans* retinal back to 11-*cis* retinal for rhodopsin regeneration. OS are continuously renewed, with aged membrane removed at the distal end by phagocytosis and new membrane added at the proximal end through OS disk morphogenesis linked to protein trafficking. The molecular basis for disk morphogenesis remains to be defined in detail although several models have been proposed, and molecular mechanisms underlying protein trafficking are under active investigation. The aim of this Cell Science at a Glance article and the accompanying poster is to highlight our current understanding of photoreceptor structure, phototransduction, the visual cycle, OS renewal, protein trafficking and retinal degenerative diseases.

KEY WORDS: Disk morphogenesis, Photoreceptors, Phototransduction, Protein trafficking, Retinal degenerative diseases, Visual cycle

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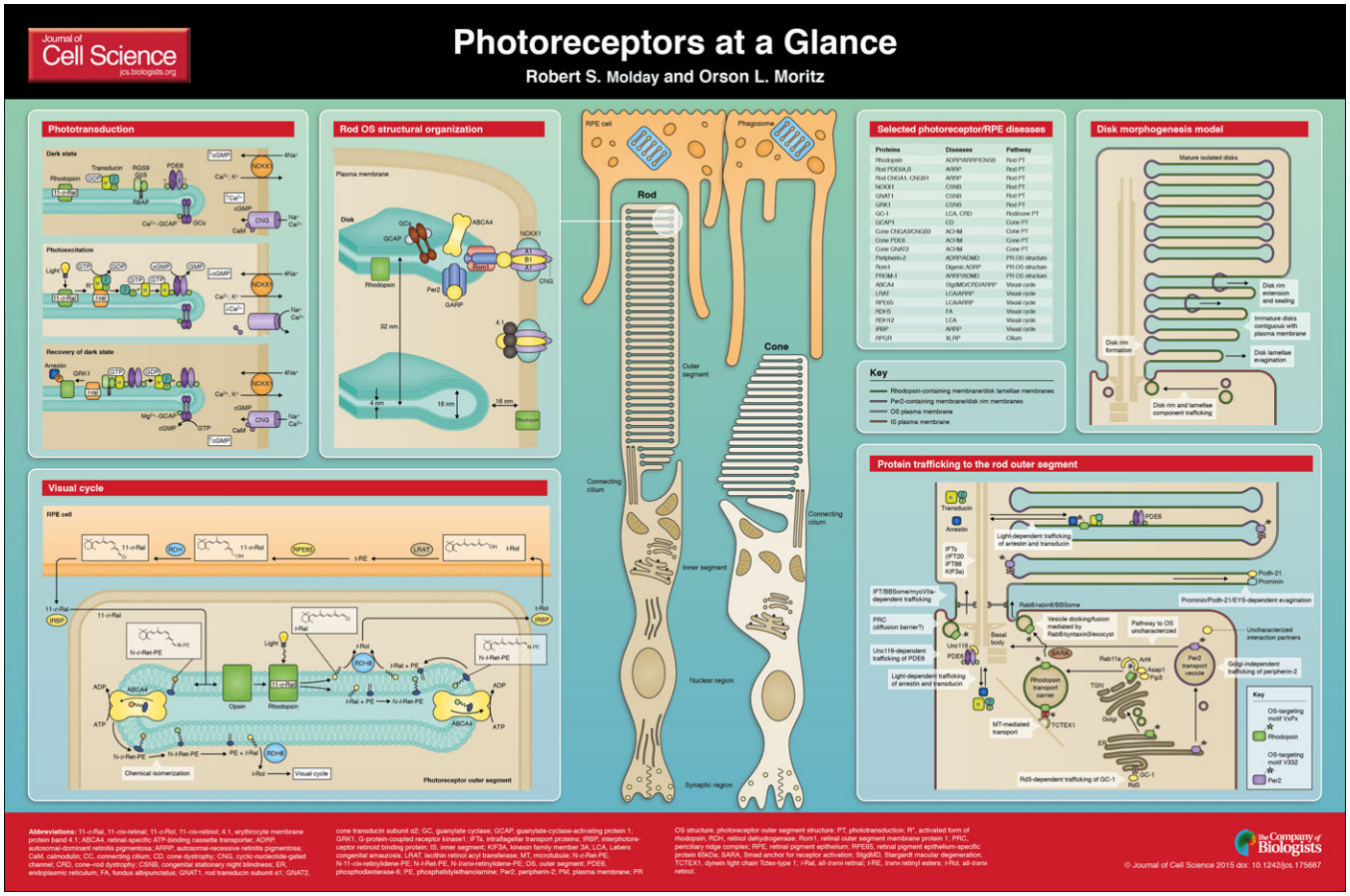
Introduction

Rod and cone photoreceptors are specialized neurons that function in the initial step of vision. These light-sensitive cells lie at the back of the retina adjacent to the retinal pigment epithelium (RPE), a cell layer that is vital for the survival of photoreceptors. Rod cells are highly sensitive to light and operate under dim lighting conditions. Cone cells function under ambient and bright lighting conditions, exhibit rapid responses to variations in light intensity, and are responsible for color vision and high visual acuity. The human retina contains 120 million rod cells and 6 million cone cells, with the latter concentrated in the central or macula region of the retina.



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Both rods and cones are highly compartmentalized in structure and function. They consist of five principal regions: outer segment (OS), connecting cilium (CC), inner segment (IS), nuclear region and synaptic region (see poster). The OS functions in the capture of light and its conversion into electrical signals in a process known as phototransduction. The CC connects the OS with the IS, allowing for the trafficking of specific proteins to the OS. The IS contains the metabolic and biosynthetic machinery of the cell including the mitochondria, endoplasmic reticulum, Golgi complex, lysosomes and other subcellular organelles. The nuclear region is continuous with the inner segment and houses the nucleus. The photoreceptor finally terminates in the synaptic region, which consists of synaptic vesicles and a ribbon synapse for transmission of the neurotransmitter glutamate from photoreceptors to bipolar cells and other secondary neurons.

The OS of rod photoreceptors has been the focus of numerous molecular, cellular, biochemical and physiological studies owing to its unique structure, accessibility, ease of isolation, and importance in the visual response, membrane renewal and retinal diseases. In this Cell Science at a Glance article and poster, we provide an overview of our current understanding of the molecular and cellular organization of photoreceptors with emphasis on the mechanisms underlying phototransduction, the visual cycle, OS structure and morphogenesis, and protein trafficking. We also highlight key proteins that have been associated with retinal degenerative diseases.

Structural organization and protein composition of the rod OS

The OS of the rod cell is a cylindrical structure consisting of a plasma membrane (PM) that encloses an ordered stack of over 1000 closely spaced disks. The length and diameter of the OS varies for different vertebrates. Mammalian rod OS typically have a length of 20–30 µm and a diameter of 1.2–2.0 µm (Gilliam et al., 2012; Nickell et al., 2007). Each disk is a closed structure and consists of two flattened membranes that are circumscribed by a hairpin rim region (see poster). The photopigment rhodopsin, which comprises >85% of the disk membrane protein, is arranged in the form of higher-order oligomers in the disk lamellae at a density of >25,000 rhodopsin molecules/µm^2 (Fotiadis et al., 2003; Gunkel et al., 2015; Liebman and Entine, 1974). The disk rim contains a number of specialized membrane proteins, the Per2–Rom1 complex consisting of the two tetraspanin membrane proteins Per2 (also known as PRPH2) and Rom1 that generate the highly curved disk rim (Clarke et al., 2000; Goldberg and Molday, 1996; Kevany et al., 2013; Khattree et al., 2013), the retinal-specific ATP-binding cassette transporter ABCA4 that facilitates the clearance of retinoids from disk membranes (Illing et al., 1997; Molday et al., 2009; Quazi and Molday, 2014; Sun et al., 1999; Weng et al., 1999), and members of the guanylate cyclase family GC-1 and GC-2 (also known as GUCY2D and GUCY2F respectively) that catalyze the synthesis of cyclic guanosine monophosphate (cGMP) from GTP (Karan et al., 2010, 2011; Nemet et al., 2015; Yang et al., 1995) (see poster). Per2 is most crucial for OS biogenesis and structure because deficiency in Per2, as found in *rds* mice, results in the absence of rod and cone OS (Arikawa et al., 1992; Connell et al., 1991; Sanyal and Jansen, 1981; Travis et al., 1989), and mutations in the gene encoding Per2 cause autosomal-dominant retinitis pigmentosa (ADRP) and macular dystrophy in humans (Farrar et al., 1991; Kajiwara et al., 1994, 1991; Wells et al., 1993). Proteomic analysis and biochemical studies have further shown that disk membranes also contain R9AP (also known as RGS9BP), which anchors the GAP complex RGS9 and the long splice isoform of the type 5 G protein β subunit (Gβ5) (RGS9–Gβ5) to the disk membrane, the ATP8A2–CDC50A (also known as TMEM30A) complex that functions as a phospholipid flippase, and progressive rod-cone degeneration protein (PRCD), a small protein of unknown function that is associated with progressive rod–cone degeneration (Coleman et al., 2009; Kwok et al., 2008; Skiba et al., 2013). Disks also contain membrane-associated proteins, including the trimeric G-protein transducin, phosphodiesterase (PDE6), which is composed of two large catalytic subunits (PDE6A and PDE6B) and two regulatory subunits (PDE6C), and retinol dehydrogenase 8 (RDH8). Glutamic-acid-rich proteins (GARPs) associate with the Per2 homotetramers and Per2–Rom1 heterotetramers at the rim region of disk membranes (Körschen et al., 1999; Poetsch et al., 2001) (see poster). The PM of rod OS contains substantial amounts of rhodopsin (Molday and Molday, 1987; Nemet et al., 2015) as well as the cyclic-nucleotide-gated (CNG) channel that consists of three CNGA1 and one CNGB1 subunits, with the latter harboring an N-terminal GARP domain, and the Na^+–$Ca2^+$–K^+ exchanger (NCKX1, also known as SLC24A1) (Colville and Molday, 1996; Cook et al., 1989; Kaupp and Seifert, 2002; Reid et al., 1990; Zhong et al., 2002). The CNG channel forms a complex with NCKX1 in the PM (Bauer and Drechsler, 1992; Molday and Molday, 1998) (see poster). Thin filaments have been observed by using electron microscopy (EM) between disks and between the disk and PM (Roof and Heuser, 1982). Protein-protein interactions between the CNGB1 subunit of the CNG channel in the PM and Per2–Rom1 complex in the rim region of the disks are important in maintaining the organization of the rod OS and might represent the thin filaments observed by EM (Gilliam et al., 2012; Poetsch et al., 2001; Ritter et al., 2011; Zhang et al., 2009) (see poster). The proximity of the CNG channel–NCKX1 complex to other key phototransduction proteins such as PDE6, GCs, GCAP (guanylate-cyclase-activating protein 1) has been proposed to enhance the efficiency of phototransduction (Körschen et al., 1999; Nemet et al., 2015). Recent studies have also shown that a subset of CNG channels interact with the erythrocyte membrane protein band 4.1 (also known as EPB41), although the importance of this interaction remains to be investigated (Cheng and Molday, 2013). Cone photoreceptors have a similar structural organization, although the disks are continuous with the PM and the OS most often is of conical shape (Mustafi et al., 2009). The genes encoding some proteins, such as Per2, Rom1, GC-1, ABCA4, RDH8, RGS9, Gβ5, R9AP (i.e. RGS9–Gβ5–R9AP) and PRCD, are expressed in both rods and cones, whereas others, including those encoding opsins, CNG channels, NCKXs, PDEs and transducins, are encoded by homologous genes expressed in either rods or cones.

Phototransduction

Phototransduction in rods is initiated when light isomerizes the 11-*cis*-retinal chromophore of rhodopsin to its all-*trans* isomer that induces a conformational change (Arshavsky and Burns, 2012; Lamb and Pugh, 2006; Luo et al., 2008; Palczewski, 2014). The activated form of rhodopsin R* (also known as metarhodopsin II) catalyzes the exchange of GDP for GTP on the α-subunit of the trimeric G-protein transducin (comprising subunits α, β and γ; see poster). The α-subunit of transducin with its bound GTP dissociates from the βγ subunits and activates PDE6, a complex of one PDE6A, one PDE6B and two PDE6G subunits, leading to the hydrolysis of cGMP. Reduction in intracellular cGMP results in the closure of CNG channels within the PM and cessation of Na^+ and Ca^{2+} influx, hyperpolarization of the rod cell and inhibition of glutamate release

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at the photoreceptor synapse. The closure of CNG channels also results in a decrease in intracellular Ca^{2+} levels to below 50 nM as NCKX1 continues to efflux Ca^{2+} from the OS. Quantitative studies indicate that photoisomerization of a single rhodopsin molecule results in the activation of 16 transducin proteins in mouse rods and of 60 in frog rods (Arshavsky and Burns, 2014). Further amplification is realized through PDE6-catalyzed hydrolysis of 2000 and 72,000 cGMP molecules in mouse and frog, respectively.

The photoreceptor cell is returned to its dark state through a series of biochemical reactions (Lamb and Pugh, 2006; Pugh and Lamb, 1993) (see poster). Rhodopsin is phosphorylated by G-protein-coupled receptor kinase (GRK1) and inactivated following the binding of arrestin (Burns et al., 2006; Chen et al., 2012; Gurevich et al., 2011; Wilden et al., 1986). PDE6 is returned to its dark inactive state through the hydrolysis of GTP on the α-subunit of transducin, a reaction that is facilitated by the GTPase-activating protein (GAP) RGS9 (Arshavsky and Wensel, 2013). Cyclic GMP levels are re-established following the activation of GC through the Ca^{2+} sensors guanylate-cyclase-activating proteins (GCAPs) (Baehr and Palczewski, 2007). When cGMP levels rise, CNG channels open and return the photoreceptor to its dark, partially depolarized state. The ubiquitous Ca^{2+} sensor calmodulin (CaM) modulates the sensitivity of the channel for cGMP (Hsu and Molday, 1993). Phototransduction in cones occurs through a similar mechanism. Finally, for the regeneration of rhodopsin, all-*trans* retinal has to be converted back to 11-*cis* retinal. This occurs through a series of biochemical reactions known as the visual or retinoid cycle, which take place in both rod OS and RPE cells (Kiser et al., 2014; Saari, 2012).

Mutations within most of the phototransduction proteins have been associated with retinal diseases. Mutations in the genes encoding rhodopsin, CNGA1, CNGB1, PDE6A or PD6B cause retinitis pigmentosa (RP), whereas mutations in the genes encoding arrestin, rhodopsin kinase or NCKX1 cause congenital stationary night blindness (CSNB). Furthermore, mutations in the genes encoding cone CNG channel subunits CNGA3 and CNGB3, cone PDEH or cone transducin (GNAT2) give rise to achromatopsia, and mutations in the genes encoding in GC-1 have been linked to Leber congenital amaurosis (LCA) and cone–rod dystrophy (CRD) (see Box 1 and table within the poster).

Visual or retinoid cycle

In the conventional visual cycle, all-*trans* retinal released from rhodopsin following photoexcitation is reduced to all-*trans* retinol by RDH8 in disks (see poster). All-*trans* retinol is shuttled to RPE cells by the interphotoreceptor retinoid-binding protein (IRBP) where it is first converted to its retinyl esters by lecithin retinol acyl transferase (LRAT), before being isomerized to 11-*cis*-retinol by RPE65, oxidized to 11-*cis*-retinal by RDH5 and other RDHs, and delivered back to photoreceptors by IRBP for the regeneration of rhodopsin. However, a substantial fraction of all-*trans* retinal that is released from rhodopsin reversibly reacts with phosphatidylethanolamine (PE) to form the Schiff base adduct *N*-retinylidene-PE (*N*-ret-PE). This retinoid compound can become trapped on the luminal leaflet of disk membranes. ABCA4 actively transports or flips *N*-ret-PE to the cytoplasmic leaflet of disk membranes (Molday et al., 2009; Quazi et al., 2012) (see poster). All-*trans* retinal produced through the reversible dissociation of *N*-ret-PE is then reduced by RDH8 as part of the visual cycle. Retinal can diffuse from photoreceptor OS to the IS and RPE cells. Other RDH isozymes, including RDH12 and RDH10, protect these cellular compartments against retinal toxicity. Recent studies have shown that ABCA4 also plays a crucial role in the removal of excess 11-*cis* retinal that is not needed for the regeneration of rhodopsin (Boyer et al., 2012). ABCA4 can flip the 11-*cis* isomer of *N*-ret-PE from the luminal to the cytoplasmic leaflet of disks (Quazi and Molday, 2014). This transport function, coupled with chemical isomerization to all-*trans*-*N*-ret-PE, enables all-*trans* retinal to be reduced to all-*trans* retinol by RDH8 for entry into the visual cycle. This ensures that none of the 11-*cis* and all-*trans* retinal accumulate in disks. If these compounds are not efficiently removed, they can form toxic bisretinoid compounds, which accumulate in RPE cells upon OS phagocytosis. High levels of bisretinoids within lipofuscin deposits are found in individuals with Stargardt macular degeneration linked to mutations in the gene encoding ABCA4 as well as in *Abca4*-knockout mice (Allikmets et al., 1997; Mata et al., 2000; Molday and Zhang, 2010; Sparrow et al., 2012). In addition to the conventional visual cycle, cone photoreceptors use a modified

Box 1. Inherited retinal diseases

Inherited retinal diseases are a clinically and genetically heterogeneous group of disorders that constitute a main cause of blindness in the world (Bramall et al., 2010; Veleri et al., 2015). These disorders are typically characterized by the progressive loss in vision resulting from mutations of genes encoding proteins that are essential for photoreceptor development, function or survival. Over 238 disease-linked genes have now been identified (http://www.sph.uth.tmc.edu/Retnet/). The two principal types of retinal degenerative disease (RDD) are retinitis pigmentosa (RP) and macular degeneration (MD). RP, with a prevalence of 1 in 3500 people is typically characterized by the initial loss in night and peripheral vision due to the degeneration of rods, followed by loss in cone-mediated central vision that often leads to total blindness. RP can be inherited as an autosomal-dominant (AD) RP, autosomal-recessive (AR) RP or X-linked (XL) RP trait with ADRP accounting for 30-40% of the cases, ARRP for 50-60% and XLRP for 5-15% (Hartong et al., 2006). RP can be associated with other disorders, such as hearing loss (Ushers syndrome) and cognitive impairment, polydactylism, hypogenitalism, obesity and renal disease (Bardet-Biedl syndrome). MD is typically associated with loss in central vision with variable preservation of peripheral vision. Inherited forms of MD, often called macular dystrophies, are divided into subgroups on the basis of their clinical characteristics. Examples include Stargardt macular degeneration, Best disease, Doyne honeycomb retinal dystrophy, Sorsby fundus dystrophy, Bull's eye maculopathy, and X-linked retinoschisis. Age-related macular degeneration (AMD) is a leading cause of vision loss in the elderly. Although not considered an inherited RDD, genetic variants that encode complement factors and other proteins are known to increase one's risk of acquiring AMD (Fritsche et al., 2014). Other clinically defined inherited RDDs include cone dystrophy (CD) characterized by cone degeneration, cone-rod dystrophy (CRD) associated with cone degeneration followed by rod degeneration, and Leber congenital amaurosis (LCA), an early-onset RDD characterized by severe loss of vision at birth or within the first year of life (den Hollander et al., 2008). Congenital stationary night blindness (CSNB) is a group of nonprogressive retinal disorders characterized by impaired night vision and associated with loss in rod or both rod and cone function. Achromatopsia (ACHM) is a nonprogressive cone disorder associated with partial or complete loss in color vision. Inherited retinal diseases have been linked to mutations in proteins that play crucial roles in processes such as phototransduction; the visual cycle; outer segment (OS) structure and morphogenesis; connecting cilium structure and transport, as well as in cellular functions that include protein trafficking; protein folding and post-translational modification; protein trafficking; RNA splicing and transcription; nucleotide, carbohydrate and lipid metabolism; extracellular matrix structure; ion transport; synaptic structure and neurotransmission; and development. The molecular and cellular mechanisms by which mutations in specific genes cause photoreceptor cell death are currently under extensive investigation.

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visual cycle in which 11-*cis* retinal is resynthesized from all-*trans* retinol through a series of reactions that take place in Müller cells and cones (Mata et al., 2002). Most proteins that function in the visual cycle have been associated with retinal degenerative diseases. Mutations in the genes encoding LRAT and RPE65 have been linked to LCA, mutations in the gene encoding IRBP are associated with RP, and mutations in gene encoding RDH5 cause a rare form of CSNB termed fundus albipunctatus (FA) (Travis et al., 2007).

OS – membrane turnover and relationship to non-motile cilia

Rod and cone OS are structurally homologous to non-motile cilia. The CC, the only physical connection between OS and IS, is structurally equivalent to the ciliary transition zone (Gilliam et al., 2012). Passing through this 0.3-µm connection is an axoneme with a 9+0 arrangement of tubulin doublets that is anchored via the basal body to the ciliary rootlet, a structure that spans the length of the IS. The CC has been imaged in three dimensions by using cryo-EM (Gilliam et al., 2012). Most components of the CC are always present in other non-motile cilia, although unique components, such as RPGRIP and a splice variant of RPGR (Hong et al., 2001), are present. Profuse bi-directional trafficking of soluble and transmembrane proteins occurs through the CC. Owing to the high volume of transport (Besharse et al., 1977), the OS serves as a default destination for membrane proteins that lack localization information, for instance, due to mutations (Agbaga et al., 2014; Baker et al., 2008; Tam et al., 2000), with the relative degree of OS localization dependent on the rate of disk membrane synthesis (Pearring et al., 2013).

OS are rapidly renewed to ensure maximum photosensitivity, which requires 10 days in mice, rats and *Xenopus laevis* (Besharse et al., 1977; Young, 1967), but 6 weeks in *Rana pipiens*. Radiolabeling shows that disk synthesis occurs at the base of the OS (Young and Droz, 1968). Older disks are displaced distally and eventually shed in packets from the tip of the OS, where they are phagocytosed by the RPE (Kevany and Palczewski, 2010; Young and Bok, 1969). Because cone disks are not physically isolated, mixing of new and old components of the disk membrane occurs (Young, 1969); however, disk renewal, similarly, involves incorporation of new components as well as shedding and phagocytosis of a fraction of the OS membranes (Anderson et al., 1978; Hogan et al., 1974).

Already several decades ago, it has been proposed that disks originate as evaginations of the PM, which then develop a specialized rim region and, eventually, seal off completely in rods (Steinberg et al., 1980) (see poster). This model is well-supported by several lines of evidence, including EM studies (Besharse et al., 1977; Steinberg et al., 1980), incorporation of membrane-impermeable dyes, such as Lucifer yellow, into basal disks (Matsumoto and Besharse, 1985) and the presence of open contiguous disks in cones, which evolutionarily precede rods (Lamb et al., 2007). In contrast, more recently Sung and colleagues have proposed that rod disks are never continuous with the PM (Chuang et al., 2007) and originate from fusion of transport vesicles that transit the CC (Chuang et al., 2015). However, this model of disk synthesis, the evidence for which is limited to the output of a single laboratory, has been discounted by two recent findings. David Williams (Jules Stein Eye Institute, UCLA, CA) and co-workers imaged nascent disks in three dimensions by electron tomography, demonstrating both the presence of open disks and the source of enclosed disk profiles in standard electron micrographs (David Williams, personal communication). Ding et al. (2015) demonstrated that nascent disks are accessible to membrane-impermeable tannic acid, even in cases where 2D electron micrographs indicate enclosure by a plasma membrane, and that even short delays in fixation can generate vesicular structures. Moreover, structural studies indicate that vesicles of the dimensions observed could not pass through the basal body (Jin et al., 2010).

At least two membrane proteins are exclusively found at the site of, and are likely to be involved in, disk synthesis within rods and cones: prominin-1, which is also associated with membrane evaginations in other cell types (Han et al., 2012; Maw et al., 2000), and pcdh-21 (also known as CDHR1), a photoreceptor-specific protocadherin (Rattner et al., 2001). These proteins form a complex of unknown function (Yang et al., 2008) that also includes the extracellular soluble protein eyes shut (EYS) (Nie et al., 2012).

Protein trafficking to the OS

Trafficking of several proteins between OS and IS has been examined in some detail, including that of rhodopsin, Per2, arrestin, transducin, guanylate cyclase and phosphodiesterase (Pearring et al., 2013). Rhodopsin, the most abundant protein in rod OS, is a transmembrane protein with a C-terminal ciliary targeting signal (Tam et al., 2000) that is also present in cone opsins. The large unidirectional flow of rhodopsin to the OS makes it a cargo of interest for ciliary trafficking studies (Wang and Deretic, 2015). Rhodopsin trafficking involves crossing an uncharacterized diffusion barrier that separates OS and IS PM components (Jin et al., 2010). Vesicles transporting rhodopsin fuse with the IS PM at a specialized convolution at the base of the CC, termed the periciliary ridge complex (Papermaster et al., 1985; Peters et al., 1983). This structure is hypertrophied in frog rods, but analogous structures are present in mammalian photoreceptors and other primary cilia. Small G-proteins are associated with membranes that contain newly synthesized rhodopsin (Deretic et al., 1995); these have also been implicated in rhodopsin trafficking following both *in vivo* and *in vitro* investigations that demonstrated an inhibition of trafficking by dominant-negative Rab8 (Moritz et al., 2001) and a direct interaction of Arf4 and Rab11 with the ciliary targeting signal (Deretic et al., 2005; Reish et al., 2014). Rab8 is also implicated through association of the Rab8 effector rabin8 with the multiple-protein complex comprised of seven Bardet–Biedl syndrome (BBS) proteins, the BBSome, which constitutes a coat complex coat that is involved in ciliary trafficking (Nachury et al., 2007), as well as the presence of the Rab8 GEF RPGR in the CC (Murga-Zamalloa et al., 2010). Other factors implicated in rhodopsin trafficking include the t-SNARE syntaxin-3 (Mazelova et al., 2009b), the Rab11 effector FIP3 (also known as IKBKG), the ArfGAP ASAP1 (Mazelova et al., 2009a), and cytoplasmic dynein (Tai et al., 1999). There is conflicting evidence as to whether intraflagellar transport IFT – which is mediated by kinesin-2 motor proteins – is involved, and kinesin-2 might be more crucial for cone opsin transport (Avasthi et al., 2009; Bhowmick et al., 2009; Insinna and Besharse, 2008; Jiang et al., 2015a,b; Keady et al., 2011; Marszalek et al., 2000; Trivedi et al., 2012). A distinct localization signal has also been identified in Per2 (Salinas et al., 2013; Tam et al., 2004), which is transported by a pathway that bypasses the Golgi complex (Fariss et al., 1997; Tian et al., 2014). Several proteins require cofactors for OS trafficking, including GC – which requires RD3 (Azadi et al., 2010), cone opsin (11-*cis* retinal) (Zhang et al., 2008) and phosphodiesterase (UNC119) (Zhang et al., 2011).

The soluble proteins arrestin and transducin exhibit light-dependent trafficking (Peterson et al., 2003; Sokolov et al., 2002; Whelan and McGinnis, 1988). In response to light, arrestin migrates to rod OS, whereas transducin translocates to IS. Retrograde transport of transducin is linked to saturation of phosphodiesterase and does not occur in cones unless they are genetically modified to express rod opsin (Lobanova et al., 2010). Arrestin transport was originally thought to be caused by its binding to phosphorylated rhodopsin.

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However, it is more likely to be an active transport mechanism that ensures adequate quenching of phototransduction, possibly triggered by a phospholipase C cascade (Orisme et al., 2010), as rhodopsin phosphorylation is not required (Calvert et al., 2006; Mendez et al., 2003; Strissel et al., 2006). Tubulin has been proposed to bind with low affinity to arrestin in the IS (Nair et al., 2005).

Conclusions and perspectives

Considerable progress has been made in the characterization of photoreceptor cells and their role in the initial step of the visual process. Most of the rod and cone proteins that play crucial roles in OS structure, phototransduction and the visual cycle have been identified and characterized at molecular and cellular levels. The renewal of rod and cone OS has also been elucidated in detail at cellular level. However, the molecular mechanisms responsible for OS phagocytosis by RPE and disk morphogenesis require more-detailed studies. Additional studies are also needed to define the molecular and cellular basis for protein trafficking and sorting within photoreceptors as many of the proposed mechanisms are controversial and lacking in detail. Finally, further studies are needed to elucidate the molecular and cellular mechanisms responsible for inherited retinal degenerative diseases, and the biochemical pathways important for photoreceptor survival and photoreceptor cell death. Information from these studies is crucial for the development of rational therapeutic approaches to slow or prevent vision loss in individuals who suffer from various retinal diseases.

Competing interests

The authors declare no competing or financial interests.

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