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Ciliary signaling cascades in photoreceptors

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ABSTRACT

For being a polarized neuron and having a sensory cilium, photoreceptors attract remarkable attention. This is due their highly polarized structure and active visual signal transduction cascades and for the enrichment of complex networks of proteins in the cilium. Structural and functional maintenance of the photoreceptor sensory cilium, also called outer segment, ensures that light signal is received and relayed appropriately to the brain. Any perturbations in the protein content of the outer segment result in photoreceptor dysfunction, degeneration and eventually, blindness. This review focuses on the importance of photoreceptor sensory cilium to carry out signal transduction cascade for vision.

1. Introduction to cilia

The primary cilium is a microtubule based membranous extension that grows from a basal body (or mother centriole) in nearly all cell types during interphase (Kobayashi & Dynlacht, 2011). Ciliogenesis is initiated by the attachment of the mother centriole (which becomes the basal body) to a ciliary vesicle followed by nucleation of microtubules to form the axoneme (Sorokin, 1962). The base of the axoneme is structurally distinct and consists doublet microtubules as opposed to triplet microtubules observed in the basal body. This region is called the transition zone (TZ) and consists of Y-linkers that connect the TZ microtubules to the ciliary membrane (Gilula & Satir, 1972). There is no known protein synthesis machinery within the cilium; therefore, the components that make or maintain the cilia must be delivered to the cilia. Cilia are built and maintained by an elaborate and evolutionarily conserved bidirectional transport system called Intraflagellar Transport (IFT). The IFT was first described elegantly in green alga *Chlamydomonas reinhardtii* (Kozminski, Diener, & Rosenbaum, 1993; Kozminski et al., 1993). The IFT is carried out by two distinct multiprotein complexes, IFT-A and IFT-B and microtubule based motor assemblies Kinesin-2 (anterograde) and cytoplasmic dynein (retrograde) (Rosenbaum & Witman, 2002). IFT-B and Kinesins are involved in the anterograde transport of cargo whereas IFT-A and the cytoplasmic dynein carry out retrograde movement of the precursors and other products back towards the basal body. Consistent with this function, inactivation of IFT-B and the Kinesin complex results in defective generation of cilia. However, role of the retrograde transport complex in cilia formation or function is not clear; nonetheless, inactivation of the IFT-A subunits as well as cytoplasmic dynein can result in defective cilia.

There are two types of cilia: motile cilia and immotile (primary or sensory) cilia. Motile cilia contain a 9 + 2 array of microtubules (9 outer and 2 central microtubules) as well as outer and inner dynein arms, which provide motility and modulate beating of these cilia. On the other hand, primary cilia lack the central microtubule pair and the dynein arms (9 + 0 array of microtubules) (Satir & Christensen, 2008). Motile cilia are detected in a tissue restricted manner, such as in propelling sperm, in embryonic node to pattern left-right asymmetry, in airway epithelial cells and in cerebrospinal fluid. Primary cilia are specialized as cellular antennae and are detected in a more ubiquitous pattern compared to motile cilia. They are involved in renal development and function, embryonic development, limb bud development and in neurosensory functions, such as hearing, smell, and sight (Anand & Khanna, 2012; Gerdes, Davis, & Katsanis, 2009; Hildebrandt, Benzing, & Katsanis, 2011). Commensurate with their near ubiquitous presence and their involvement in developmental pathways, any defects in cilia formation or function are associated with a large number severe defects, collectively called ciliopathies (Anand & Khanna, 2012;

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Badano et al., 2006; Hildebrandt, Benzing, & Katsanis, 2011). These include Bardet–Biedl Syndrome (BBS), Joubert Syndrome (JBTS), Meckel–Gruber Syndrome (MKS), and Senior–Løken Syndrome (SLSN). In addition, ciliary dysfunction is also associated with isolated disorders, such as cystic kidney disease (nephronophthisis and polycystic kidney disease) and photoreceptor degeneration (Anand & Khanna, 2012; Hildebrandt & Zhou, 2007; Pazour & Rosenbaum, 2002).

2. Retina and photoreceptors

The retina is part of the central nervous system and is located at the back of the eye. It exhibits a unique laminated structure formed by six types of neurons and one type of glia. The outermost layer of the retina consists of photoreceptors (PRs), which are the first order of neurons that respond to light. Overlaying the photoreceptors is a layer of phagocytic cells called retinal pigmented epithelium (RPE). The photoreceptors transmit the visual signal to the inner retinal neurons, which eventually transmit it to the optic nerve and the brain (Masland, 1986). There are two types of photoreceptors: rods and cones. Rod photoreceptors are sensitive to dim light and assist in dim light vision whereas cone photoreceptors are responsible for the high acuity daytime vision (Wang & Kefalov, 2011). In humans, mice and other mammals, 95–97% of the photoreceptors are rods and 3–5% are cones. The distribution of these photoreceptors in the retina is also uneven with majority of cones present in the central retina (or fovea in primates) while rods predominantly populate the peripheral retina (Carter-Dawson & LaVail, 1979). Rod and cone photoreceptors also exhibit structural differences. While all PRs have a distinct inner segment and light-sensitive outer segment (OS), rod OS is arranged in the forms of densely packed membranous disks enclosed by the plasma membrane. In contrast, cone outer segments form disk-like membranous invaginations that are not ensheathed in the plasma membrane and hence, are in direct contact with the extraphotoreceptor milieu (also called interphotoreceptor matrix).

3. Photoreceptor sensory cilium

The OS of photoreceptors is a modified sensory cilium. The cilium originates from the basal body in the apical inner segment as TZ (also called connecting cilium) (Fig. 1). The axoneme of the cilium extends into the OS and is thought to provide structural backbone to the membranous disks that are loaded with the photopigment rhodopsin and other proteins required for phototransduction (Liu et al., 2003). Photoreceptor cilia are unique in two major ways: (i) the ciliary OS membrane contains coin-stack shaped disks to increase the efficiency of signal detection and (ii) the OS disks are periodically shed distally and new disks and membrane components are renewed proximally. It is estimated that approximately 10% of the OS is shed each day and to renew the cognate membrane components, nearly 2000 opsin molecules are transported per second in a normal human photoreceptor (Besharse, Forestner, & Defoe, 1985; Besharse & Hollyfield, 1976, 1979; Besharse, Hollyfield, & Rayborn, 1977a, 1977b; Young, 1967, 1968).

4. Ciliary signaling

The ciliary membrane maintains a unique composition of peripheral and integral membrane proteins and receptors (Nachury, Seeley, & Jin, 2010). This feature makes cilia a platform to carry out diverse signaling cascades by modulating the relay of extrinsic cues to the cell interior. These pathways include sonic hgedgehog (Shh), Wnt, and Platelet derived growth factor signaling. Shh signaling is in the foundation of many developmental processes ranging from left-right asymmetry, neural tube patterning and formation of various tissues such as pancreas and lungs (Goetz & Anderson, 2010; Scholey & Anderson, 2006; Singla & Reiter, 2006; Yoder, 2006). The relay of secreted ligand Shh depends on the membrane bound receptor called patched1 (Ptch1). In the absence of the ligand, Ptch1 functions as a repressor of seven transmembrane protein Smoothened (Smo). Binding of Shh to Ptch1 results in the exit of Ptch1 from the cilium and translocation of Smo into the cilium and conversion of Gli transcription factors into

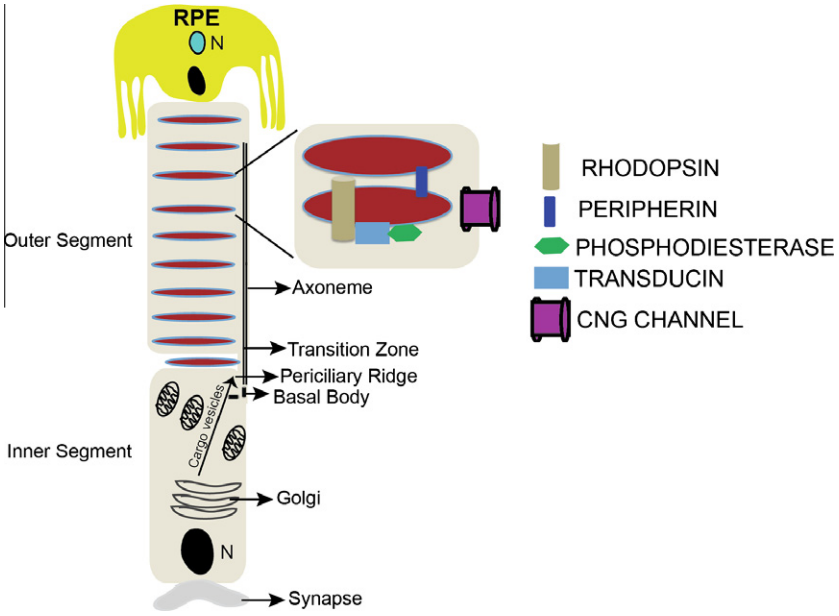

Fig. 1. Schematic representation of phototransduction components in photoreceptors. The outer segment (OS) is a modified cilium, with the basal body (BB) located at the apical region of the inner segment. The transition zone extends from the BB and gives rise to the axoneme, which continues into the outer segment. The disk membranes in the outer segment are enriched in rhodopsin and other proteins required for carrying out the phototransduction cascade. Part of the cascade also takes place in the overlaying RPE (retinal pigmented epithelium). In addition, RPE is also required for periodic disk shedding by phagocytosis. Only selected proteins in the outer segment are depicted in the inset. N: nucleus.

their activator form. The activated Gli proteins are then translocated to the nucleus to modulate gene transcription. In addition to Shh signaling, cilia are also implicated in Wnt signaling, Notch signaling, platelet derived growth factor receptor signaling as well as signaling cascades involved in *C. reinhardtii* mating and phototactic behaviors (Ezratty et al., 2011; Singla & Reiter, 2006).

Disruption of ciliary membrane protein transport affects Shh signaling and results in developmental disorders. Mice carrying mutations in IFT complex components exhibit neural patterning phenotypes, reminiscent of defective Shh signaling (Huangfu & Anderson, 2005; Liem et al., 2012). Loss of ciliary protein RPGRIP1L (NPHP8; FTM) also results in defective Gli processing and Shh signaling in mice (Vierkotten et al., 2007). Although mutations in RPGRIP1L are primarily found in MKS and JBTS patients (Arts et al., 2007; Brancati et al., 2008; Delous et al., 2007), hypomorphic variations in RPGRIP1L can affect the penetrance and severity of photoreceptor degeneration phenotype in JBTS and MKS patients (Khanna et al., 2009).

Cilia are also implicated in the modulation of Wnt signaling pathway. Discovered by Nusse and Varmus (1982), this signaling cascade is a key regulator of embryogenesis, regeneration and cancer progression. There are two types of Wnt signaling cascades: canonical (mediated by β-catenin) and non-canonical. Mechanistic details of the mode of action of these pathways have been detailed elsewhere. As Wnt signaling is also involved in retinal cell fate determination and development, defects in Wnt pathway are associated with retinal diseases, including Norrie's disease, RP, and familial exudative vitroretinopathy (Lad, Cheshier, & Kalani, 2009).

It should be noted that signaling events also take place in the RPE due to periodic uptake of distal tips of the photoreceptor OS by the RPE. These signaling events involve the α v β 5 integrin receptors and downstream activation of tyrosine kinases, such as Mer receptor tyrosine kinase (Mertk) and focal adhesion kinase. These studies highlight the importance of ciliary signaling proteins in carrying out photoreceptor development and function. These studies have been elegantly described earlier (Feng et al., 2002; Finnemann et al., 1997; Mao & Finnemann, 2012; Nandrot et al., 2006). Subsequent sections in this article will focus on the importance of ciliary proteins in regulating photoreceptor ciliary signaling cascades, specifically phototransduction. This article does not attempt to focus on the phototransduction cascade per se, which has been extensively reviewed previously. In fact, we would like to focus on the role of ciliary transport processes that assist in the recruitment of the various phototransduction signaling components from the inner segment to the outer segment.

5. Light-dependent signal transduction in photoreceptors

Photon absorption requires the presence of a photopigment. Both rods and cones have specific proteins called opsins that act as the visual pigment when bound to the chromophore. In rods, rhodopsin is the opsin that responds to light stimulus while cones express cone opsins: there are generally three types of cone opsins in humans: short wavelength or S-opsin, medium wavelength or M-opsin and long wavelength or L-opsin. Mice express only two types of cone opsins: S opsin and M opsin. Moreover, in mice, S and M opsins are co-expressed in most cones. Opsins are members of the G protein coupled receptor family of transmembrane proteins and are the most abundant protein in the OS of photoreceptors (Palczewski, 2006) {Arshavsky & Burns, 2012 #1306; Palczewski, 2012 #1307}.

In dark, the opsin is bound to the chromophore 11-cis retinal, making a visual pigment. Photon absorption results in the isomerization of 11-cis retinal (11 cis-RAL) to all-trans retinal (at-RAL), which ultimately results in conformational changes in the opsin to form an activated Meta II form of rhodopsin. Eventually, the Meta II rhodopsin decays into an inactive Meta III state with dissociation of at-RAL. This process is relatively faster in cones (within seconds) than in rods (in several minutes). The conversion of light signal into electrical signal is called phototransduction. Rhodopsin activation is followed by signal amplification and deactivation to confer reproducibility and higher demand of activity of these cells. The next step in the visual transduction cascade is activation of G protein transducing (Gt), which leads to activation of cGMP phosphodiesterase (PDE) causing hydrolysis of cGMP. Decrease in cGMP concentration results in the closure of cyclic nucleotide gated (CNG) channels, which are located at the OS plasma membrane. This results in a decrease in the inward current eliciting membrane hyperpolarization and block of glutamate release, which leads to conveying the light signal to the next order of neurons as electrical signal. The recovery after each phototransduction is essential to ensure continuous response to light. Activated rhodopsin is turned off by two steps. First addition of three phosphates by rhodopsin kinase (GRK1) and second, arrestin binds and traps the phosphorylated rhodopsin, reviewed in Wang and Kefalov (2011).

6. Transport of signaling proteins into ciliary OS

Like other cilia, PR cilia lack a protein synthesis machinery. Therefore, all its components are synthesized in the IS and have to be delivered to the basal body for eventual trafficking distally into the cilia. PRs exhibit a light dependent enrichment of selected soluble proteins in the OS: arrestin is accumulated in the OS in light and translocates to the IS in dark. On the other hand, transducin is found predominantly in the dark (Sokolov et al., 2002; Strissel et al., 2006). The mechanism of visual signal dependent enrichment of proteins in the OS is thought to be regulated by diffusion (Nair et al., 2005). It was also recently shown that soluble GFP can freely diffuse between the IS and the OS (Calvert, Schiesser, & Pugh, 2010). However, it was recently shown that light-dependent translocation of arrestin depends upon phospholipase C dependent signaling and requires ATP (Orisme et al., 2010). Membrane proteins traffic from the trans-Golgi network (TGN) as vesicles and based on their targeting sequence, undergo polarized transport to specific membrane compartments (Deretic, 1998). Although it was shown that in PRs, the OS acts as the default destination for transmembrane proteins (Baker et al., 2008), presence of ciliary targeting sequence (CTS) might ensure complete and more efficient system of delivery of key signaling molecules, such as rhodopsin to the OS. The consensus CTS described for some ciliary membrane protein is VxPx . The CTS of rhodopsin is present in its cytoplasmic tail and seems to facilitate ciliary trafficking by associating with small GTPase ARF4, ASAP1, Rab11 and other associated proteins (Deretic, Puleo-Scheppke, & Trippe, 1996; Deretic et al., 1998; Mazelova et al., 2009). Trafficking from the Golgi to the cilia also involved the IFT protein IFT20, which localizes to the Golgi as well as cilia (Follit et al., 2006; Keady, Le, & Pazour, 2011). At the cilia, rhodopsin transport vesicles recruit Rab8, which tethers the vesicle to the periciliary membrane, a privileged membrane structure at the base of the cilia. The perciliary ridge was first identified by Papermaster and colleagues (Papermaster, 2002). A number of ciliary disease proteins have been found to localize to the periciliary membrane or periciliary ridge. These include Usher syndrome protein network and RP2 (Evans et al., 2010; Maerker et al., 2008; Yang et al., 2010). The precise role of these proteins at the perciliary membrane is currently unclear; nonetheless, these proteins seem to modulate rhodopsin trafficking by regulating the structure of the connecting cilium.

Entry of proteins into the cilia is regulated by the presence of a membrane diffusion barrier or a gate in the form of TZ. The TZ

consists of unique Y-shaped linkers and contains discrete multiprotein complexes (Insinna & Besharse, 2008). The transport is facilitated by interaction of the vesicles with the TZ complexes, such as the BBSome, a complex of selected BBS proteins and the IFT machinery (Nachury et al., 2007). PRs also exhibit a unique characteristic by enriching additional GEF for Rab8, called RPGR (retinitis pigmentosa GTPase regulator) (Hong et al., 2003; Khanna et al., 2005; Murga-Zamalloa, Atkins, et al., 2010). Although RPGR is widely expressed, its enrichment in the PRs indicates its role in increasing the efficiency or specificity of membrane protein trafficking to the OS. Commensurate with this, mutations in RPGR are a major cause of inherited retinal degenerative disease retinitis pigmentosa in humans (Shu et al., 2007).

In addition to rhodopsin, the OS is enriched in other components of the phototransduction cascade, such as GRK1, CNG, and phosphodiesterases. The transport of these proteins to the OS is equally important for normal function and maintenance of the OS. Remarkable studies have shown that cone and rod photoreceptors possess distinct transport machinery and pathways for the trafficking of OS proteins (Zhang et al., 2007, 2008, 2011). These data add to the complex ciliary signaling cascades that are at work in photoreceptors. The presence of a large array of TZ protein complexes might provide a platform to direct the trafficking of specific membrane proteins by loading them onto distinct IFT particles.

7. Concluding remarks

The property of PRs to stringently regulate immense protein delivery at the base of the cilium, entry into the OS and eventual shedding of the ciliary tips makes it an attractive model system to not only examine regulation of ciliary trafficking but also to understand how terminally differentiated and polarized neurons maintain their structure and function throughout the life span of an organism. We are now beginning to understand the complexities of the TZ protein assemblies of photoreceptors with at least two discrete ciliary protein complexes identified as part of RPGR-interactome (Murga-Zamalloa, Desai, et al., 2010). How such elaborate protein complexes are assembled and transported to the OS requires further detailed studies in model organisms.

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