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Tackling Primary Cilia Dysfunction in Photoreceptor Degenerative Diseases of the Eye

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Perception of what is occurring around us relies extensively on our senses, such as vision, smell and touch. Among these, vision attracts remarkable attention. The ability to see makes us appreciate life. For years, investigators have been seeking answers to remarkable capabilities of the eye to perceive and interpret light signal and any kind of disturbances causing loss of vision and degenerative ocular diseases. Answers to such questions are essential to develop a cure for people suffering from dysfunction of visual process. This editorial summarizes recent trends in the development of our understanding of a class of degenerative diseases of eye, which are caused by defects in polarized protein trafficking in photoreceptors, the light-sensing neurons in the retina.

The cell is a complex entity that defines the very basis of our existence. There are various types of cells existing in the human body that are characterized by specific roles and functions, allowing us to live a life of versatility. Photoreceptors are a particular kind of specialized neuronal cells located in the retina of the eye, essential for vision. There are two types of photoreceptors, rods and cones, each specializing in the biological processing of different wavelengths of light. Photoreceptors contain the visual pigment rhodopsin (for rods) and cone opsins (cones) that respond to light. Without photoreceptors, it is impossible for the human eye to accomplish sight. A majority of inherited blindness disorders are caused by the degeneration or dysfunction of photoreceptors. These include Retinitis Pigmentosa, Leber congenital amaurosis, and congenital stationery night blindness [1–4]. No treatment or cure is currently available for such blinding disorders.

Photoreceptors are compartmentalized neurons with two distinct segments : the inner segment and the light-sensing outer segment (OS). The OS is a modified cilium formed by microtubule-based extension of the plasma membrane from the mother centriole, also called basal body. Although cilia are present in almost all cell types, including neurons, the ciliary OS is unique in two ways: (i) the distal cilium contains membranous discs that are loaded with the photopigment as well as other components of the phototransduction cascade and (ii) the distal tips of the OS are periodically shed with new membranes and other components added proximally from their site of synthesis in the inner segment. Consistently, photoreceptors undergo immense protein and membrane synthesis and polarized trafficking to the cilia to carry out the visual signaling cascades. Any defects in the formation or maintenance of the cilia result in photoreceptor degeneration and blindness. Commensurate with this, photoreceptor degeneration is frequently observed in other ciliary disorders, collectively known as ciliopathies. These include Meckel-Gruber Syndrome, McKusick-Kaufman Syndrome, Senior-Loken Syndrome, Joubert Syndrome, and Bardet-Biedl

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Syndrome. Common characteristics of these heritable diseases consist of primarily photoreceptor degeneration, along with polydactyly, selective abnormalities in females and males, and malformations of organs such as the brain, kidneys and liver [5–9]. The occurrence of these degenerative diseases in individuals severely impacts the quality of life.

In order to tackle cilia-dependent photoreceptor degeneration, it is essential to ascertain the components of cilia and their mechanism of action. Concomitantly, using large-scale gene identification strategies will also assist in the identification of disease genes associated with ciliopathies and retinal degeneration. Advances in genomic and proteomic techniques have positively impacted our progress in confronting these disorders. While whole genome sequencing has helped in identifying causative genes as well as modifying alleles, proteomic analysis has revealed the composition of discrete protein complexes that can work in concert with each other to orchestrate protein trafficking in photoreceptors and other ciliated cells. A majority of the components of these protein complexes are ciliopathy-associated proteins or are candidate disease proteins [10–17]. As steady improvement in gene identification and proteomic strategies progresses, so does hope for individuals who inherit these unruly disorders around the world.

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References

1. Daiger SP, Bowne SJ, Sullivan SL. Perspective on genes and mutations causing retinitis pigmentosa. Arch Ophthalmol. 2007; 125:151–158. [PubMed: 17296890]
2. Heckenlively JR, Yoser SL, Friedman LH, Oversier JJ. Clinical findings and common symptoms in retinitis pigmentosa. Am J Ophthalmol. 1988; 105:504–511. [PubMed: 3259404]
3. Kefalov VJ. Rod and cone visual pigments and phototransduction through pharmacological, genetic, and physiological approaches. J Biol Chem. 2012; 287:1635–1641. [PubMed: 22074928]
4. Koenekoop RK. An overview of Leber congenital amaurosis: a model to understand human retinal development. Surv Ophthalmol. 2004; 49:379–398. [PubMed: 15231395]
5. Anand M, Khanna H. Ciliary transition zone (TZ) proteins RPGR and CEP290: role in photoreceptor cilia and degenerative diseases. Expert Opin Ther Targets. 2012; 16:541–551. [PubMed: 22563985]
6. Besharse JC, Baker SA, Luby-Phelps K, Pazour GJ. Photoreceptor intersegmental transport and retinal degeneration: a conserved pathway common to motile and sensory cilia. Adv Exp Med Biol. 2003; 533:157–164. [PubMed: 15180260]
7. Besharse JC, Hollyfield JG. Turnover of mouse photoreceptor outer segments in constant light and darkness. Invest Ophthalmol Vis Sci. 1979; 18:1019–1024. [PubMed: 478775]
8. Gerdes JM, Davis EE, Katsanis N. The vertebrate primary cilium in development, homeostasis, and disease. Cell. 2009; 137:32–45. [PubMed: 19345185]
9. Ware SM, Gunay-Aygun M, Hildebrandt F. Spectrum of clinical diseases caused by disorders of primary cilia. Proc Am Thorac Soc. 2011; 8:444–450. [PubMed: 21926397]
10. Garcia-Gonzalo FR, Corbit KC, Sirerol-Piquer MS, Ramaswami G, Otto EA, et al. A transition zone complex regulates mammalian ciliogenesis and ciliary membrane composition. Nat Genet. 2011; 43:776–784. [PubMed: 21725307]
11. Murga-Zamalloa C, Swaroop A, Khanna H. Multiprotein Complexes of Retinitis Pigmentosa GTPase Regulator (RPGR), a Ciliary Protein Mutated in X-Linked Retinitis Pigmentosa (XLRP). Adv Exp Med Biol. 2010; 664:105–114. [PubMed: 20238008]
12. Murga-Zamalloa CA, Desai NJ, Hildebrandt F, Khanna H. Interaction of ciliary disease protein retinitis pigmentosa GTPase regulator with nephronophthisis-associated proteins in mammalian retinas. Mol Vis. 2010; 16:1373–1381. [PubMed: 20664800]

13. Murga-Zamalloa CA, Swaroop A, Khanna H. RPGR-containing protein complexes in syndromic and non-syndromic retinal degeneration due to ciliary dysfunction. J Genet. 2009; 88:399–407. [PubMed: 20090203]

14. Nachury MV, Loktev AV, Zhang Q, Westlake CJ, Peränen J, et al. A core complex of BBS proteins cooperates with the GTPase Rab8 to promote ciliary membrane biogenesis. Cell. 2007; 129:1201–1213. [PubMed: 17574030]

15. Pazour GJ, Agrin N, Leszyk J, Witman GB, et al. Proteomic analysis of a eukaryotic cilium. JCB. 2005; 170:103–113. [PubMed: 15998802]

16. Sang L, Miller JJ, Corbit KC, Giles RH, Brauer MJ, et al. Mapping the NPHP-JBTS-MKS Protein Network Reveals Ciliopathy Disease Genes and Pathways. Cell. 2011; 145:513–528. [PubMed: 21565611]

17. Zaghloul NA, Katsanis N. Functional modules, mutational load and human genetic disease. Trends Genet. 2010; 26:168–176. [PubMed: 20226561]