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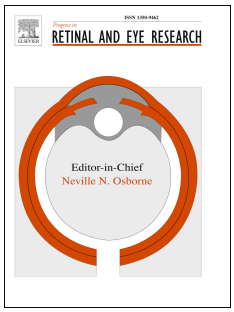

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PII: S1350-9462(16)30041-6

DOI: 10.1016/j.preteyeres.2016.06.002

Reference: JPRR 634

To appear in: *Progress in Retinal and Eye Research*

Received Date: 29 April 2015

Revised Date: 14 June 2016

Accepted Date: 20 June 2016

Please cite this article as: Wensel, T.G., Zhang, Z., Anastassov, I.A., Gilliam, J.C., He, F., Schmid, M.F., Robichaux, M.A., Structural and molecular bases of rod photoreceptor morphogenesis and disease, *Progress in Retinal and Eye Research* (2016), doi: 10.1016/j.preteyeres.2016.06.002.

Structural and Molecular Bases of Rod Photoreceptor Morphogenesis and Disease

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Abstract

The rod cell has an extraordinarily specialized structure that allows it to carry out its unique function of detecting individual photons of light. Both the structural features of the rod and the metabolic processes required for highly amplified light detection seem to have rendered the rod especially sensitive to structural and metabolic defects, so that a large number of gene defects are primarily associated with rod cell death and give rise to blinding retinal dystrophies. The structures of the rod, especially those of the sensory cilium known as the outer segment, have been the subject of structural, biochemical, and genetic analysis for many years, but the molecular bases for rod morphogenesis and for cell death in rod dystrophies are still poorly understood. Recent developments in imaging technology, such as cryo-electron tomography and super-resolution fluorescence microscopy, in gene sequencing technology, and in gene editing technology are rapidly leading to new breakthroughs in our understanding of these questions. A summary is presented of our current understanding of selected aspects of these questions, highlighting areas of uncertainty and contention as well as recent discoveries that provide new insights. Examples of structural data from emerging imaging technologies are presented.

Keywords: photoreceptor, cryo-electron tomography, retinal imaging, retinal degeneration, disease mechanisms, ciliopathies

Highlights

- Review of historical and most recent structural studies of vertebrate rod cells
- Current state of understanding of basal disk structure and morphogenesis
- Cryo-electron tomography and superresolution microscopy of rods
- Advances in understanding of cilium-associated structures
- BBSome structural and functional insights
- Current understanding and uncertainties in mechanisms of rod dystrophies

Abbrevations:

ADRP, autosomal dominant retinitis pigmentosa; BBS, Bardet-Biedl syndrome, BBSome, membrane coat complex formed by BBS gene products; Cryo-ET, cryo-electron tomography; miniSOG, mini singlet oxygen generator, a fluorescent flavoprotein engineered from *Arabidopsis* phototropin; PALM, photactivated localization microscopy; RP, retinitis pigmentosa; SEM, scanning electron microscopy; SIM, structured illumination microscopy; SNAP tag, fusion to a 20 kDa mutant of the DNA repair protein O^6-alkylguanine-DNA alkyltransferase that allows covalent labeling with with benzylguanine derivatives; STED, stimulated emission depletion; STORM, stochastic optical reconstruction microscopy; TEM, transmission electron microscopy; TPR, tetratricopeptide repeats; UPR, unfolded protein response.