LIFE SAFETY AND SECURITY

open access

Health security

Minireview

THE BALANCE BETWEEN EYE – RELATED PATHWAYS REGULATES RETINITIS PIGMENTOSA ONSET: A REVIEW OF MOLECULAR MECHANISMS

Luigi Donato[1,2], Concetta Scimone[1,2], Simona Alibrandi[1], Rosalia D'Angelo[1], Antonina Sidoti[1,2]

[1] Department of Biomedical and Dental Sciences and Morphofunctional Images, Division of Medical Biotechnologies and Preventive Medicine, University of Messina, Messina, Italy

[2] Department of Cutting-Edge Medicine and Therapies, Biomolecular Strategies and Neuroscience, Section of Neuroscience-applied Molecular Genetics and Predictive Medicine, I. E. ME. S. T., Palermo, Italy

Correspondence:
Luigi Donato
e-mail: luigidonato@iemest.eu

Received: November 24th, 2018
Revised: November 29th, 2018
Accepted: November 30th, 2018

Abstract

Retinitis pigmentosa is a heterogeneous eye disease group with a relatively high prevalence and a frequent onset at the middle age. Clinical observation of the wide spectrum of this pathology has been efficient, such as their genetic analysis, and a large catalogue of implicated loci has emerged. In addition to locus and allelic heterogeneity, along with allelic disorders, the complexity of retinitis pigmentosa is related to the actual lack of knowledge on all possible causative genes and their function. Such scenario implies that retinitis pigmentosa pathogenesis is not well understood, thus the research of new involved biochemical pathways is vital. In this review, we consider the architecture of genetic aspects that influence retinal degeneration, analyzing main biochemical pathways (such as inflammation, circadian rhythms, fatty acid metabolism, proteostasis, vesicular trafficking, phototransduction, RNA processing, extracellular matrix remodeling, cellular cycle regulation, etc.) implicated in photoreceptor degeneration via RPE impairments.

Keywords

Retinitis pigmentosa, pathway, apoptosis, cell death, oxidative stress

Introduction

Retinitis pigmentosa (RP) represents a wide group of chronic and hereditary disorders affecting the retina, which constitute an important source of disability. The cytological targets of these disorders usually regard photoreceptors (PRs) and retinal pigment epithelium (RPE), although other retinal cytotypes are not excluded. In detail, RPE provides many vital functions for photoreceptor cells, such as involvement in visual cycle [1], metabolite transport and photoreceptor excitability [2], phagocytosis of photoreceptor outer segments (POSs) [3], secretion of growth factors [4], and oxidative stress protection [5]. The inherited and multifactorial forms of RP are very heterogeneous, but they share a key feature that accounts for most of the visual disability — the loss or impairment of PRs as a primary or secondary event [6]. Clinical observation of the wide spectrum of PR defects has been efficient, such as their genetic analysis, and a large catalogue of implicated loci has emerged. In addition to locus and allelic heterogeneity, along with allelic disorders [7], the complexity of RP is due to the actual lack of knowledge on all possible causative genes and their function. In this paper, we consider the architecture of genetic aspects that influence retinal degeneration, analyzing main biochemical pathways implicated in photoreceptor degeneration via RPE impairments.

Retinal architecture

The specific organization of the human retina is finely adapted to capture and processing visual signals, but such structure also makes it uniquely vulnerable to impairment. Retina is made of an outer cell monolayer, the retinal pigment epithelium (RPE), and of an inner neural retina, consisting of a trilaminar network of different neuronal types with their connections. The outer

layer of neural retina presents photoreceptors with light – sensitivity ability, rods and cones, whose apical outer segments are densely packed with membranes holding the visual pigment opsin, covalently bound to the light-sensitive chromophore 11-cis retinal. The inner nuclear and ganglion cells process the light signals produced by PRs and transmit them through the optic nerve to the brain. In humans, the central portion of the retina is called "macula", and is specialized for high acuity vision. At the center of the macula is the fovea, which only contains cones. There is a close interdependence among RPE and PRs, so dysfunction in any of such components can cause secondary dysfunction in the others.

Pathways to photoreceptor apoptosis

Genes involved in PR degeneration affect almost all aspects of cellular physiology. Mutations impairing PR-unique functions, such as visual cycle or phototransduction, represent the most numerous ones, followed by variants affecting more general functions, such as lipid metabolism, protein folding or extracellular matrix. Interestingly, the highest number of disease-causing genes is involved in PR ciliary function. However, the final integration pathway is represented by PR apoptosis, that leads to retinitis pigmentosa onset. Now the most analyzed pathways associated to RP will be discussed.

Inflammation. Probably, an initial aggressive response by preformed cellular mediators, like histamine and lysosomal enzymes, is followed by a slow activation of inactive mediators of the fluid phase (e. g. complement and kinin system). In RPE of several RP patients, inflammation could involve the innate immunity with complement system and the inflammasome [8]. This could be a protective response in early RP; however, the recruitment of macrophages that accumulate in Bruch's membrane, potentially increases inflammasome activity, causing tissue damaging [9]. Moreover, it was recently showed that altered autophagy or mitophagy in RPE cells led to recruitment of macrophages with consequent inflammasome activation, promoting RPE and photoreceptor degeneration [10].

Mitochondrion. The outer retina presents a high metabolic demand, associated with a huge number of mitochondria in the RPE and photoreceptors that ensure a high ATP production required for cell activities and survival [11]. The high metabolic rate of retina cells is an intrinsic challenge for oxidative stress, because reactive oxygen species (ROS) represent an important product of mitochondrial metabolism [12]. Moreover, mutations in mtDNA could lead to retinal degeneration [13]. Probably, an increase of p53 located to, or near, the outer membrane where it interacts with proteins of the Bcl-2 family to promote mitochondrial outer membrane permeabilization (MOMP), triggering the release of proapoptotic factors from the intermembrane space.

RNA Processing. Alterations in pre – mRNA splicing can induce a cytotype – specific defect, especially in tissue like retina, in which there is a high number of mature mRNA derived from alternative splicing [14]. Consequently, vulnerability of retinal cells to splicing factor impairments might result from an unsatisfied requirement for the production of sufficient amounts of needed retinal mRNAs. Moreover, additional mechanism by which damaged U4/U6.U5 triple small nuclear ribonucleoprotein (tri – snRNP) complex could influence the fate of the mRNAs produced is the deposition of the exon junction complex on the spliced mRNA [15]. RNA maturation, especially 3' polyadenylation and 5' capping of pre – mRNA, probably represents one of the first and the most sensible step of genetic information flow. Thus, enzymes involved in maturation process could be immediately altered by a serious stress like oxLDL presence; this scenario leads cells to death, that means that only survived ones are able to continue the genetic flow, with a reduced number of post – transcriptional enzyme which could still be the target of induced stress.

Circadian Rhythms. The neural retina and the underlying RPE are structurally and functionally tightly linked. This relationship is essential for vision, while the diurnal and circadian rhythmicity of the RPE is needed for photoreceptor support and retinal function [16]. Main task of the adjacent RPE is to phagocytize shed photoreceptors outer segments (POSs) and to digest or recycle their components [17]. A dysregulation of this processes, synchronized under circadian control and triggered by the dark/light periods of the daily rhythm [18], is sufficient to induce rapid photoreceptor degeneration by disk shedding

[19]. Moreover, alterations such as impaired digestion or delayed termination of shedding in the RPE, can determine the accumulation of lipofuscin, leading to cell death and to the development or progression of RP [20]. Additionally, melatonin and dopamine, two regulatory signals synthesized and produced under circadian control by photoreceptors [21], seems to be involved in the control of circadian POS shedding and RPE phagocytosis.

Epigenetic. Exposure to oxidative agents induces epigenetics modifications, especially DNA methylation, triggered by the hypoxia condition [22]. Selective inhibition of DNA methyltransferases (DNMTs) in rd1 organotypic retinal explants resulted in a substantial reduction of photoreceptor cell death; at the same time, binding sites of several important transcription factors for genes involved in retinal development were hypermethylated in the mutant model due to up-regulation of other DNMTs. Moreover, demethylation of Ten-eleven translocation (TET) enzymes promoters associated with the Hypoxia Inducible Factors 1 and 2 (HIF-1, -2) is involved in specific DNA hypomethylation in chemical hypoxia of RPE cells [23]. Furthermore, recent data have revealed epigenetic derangements as a potent biologic switch for chronic inflammation and cell survival which are relevant therapeutic targets for treatment of many retinal degenerations [24].

Fatty acids metabolism. Fatty acids modulate cell loss observed in RP and other degenerative eye diseases. n–6 polyunsaturated fatty acids (PUFAs) cause deleterious consequences, while n–3 PUFAs result in beneficial effects on the retina [25]. Specifically, docosahexaenoic acid (DHA) is known to be effective in rescuing photoreceptor cells from damage [26]. Increased dietary intake of long – chain polyunsaturated fatty acids (LC–PUFAs), localized in retinal rod outer segment, prolongs photoreceptor cell life in a transgenic model of RP rats [27]. Initially, induced oxidative stress could determine the peroxidation of the LC–PUFAs, such as the exquisitely sensitive DHA. Afterwards, retinal biosynthesis of lipofuscin and its accumulation in the RPE cells is consequence of both visual processes taking place in photoreceptor – RPE functional complex and metabolic insufficiency of RPE lysosomal compartment.

Cytoskeleton and Trafficking. Various genes are known to be involved into retinal vesicular trafficking and cytoskeleton rearrangement [28]. Retinitis Pigmentosa GTPase Regulator (RPGR) mutations lead to an impaired cilia formation and to dysregulation of actin stress filaments that, in the retina, could compromise the nascent photoreceptor disc development [29]. Defects in Family With Sequence Similarity 161 Member A (FAM161A), a member of the recently recognized Golgi – centrosomal interactome which probably binds to and stabilizes microtubules, and that is localized at the connecting cilium and ciliary basal body of human photoreceptors, cause RP [30]. The Retinitis Pigmentosa 2 (RP2) regulation of Arl3 is important for maintaining Golgi cohesion, facilitating the transport and docking of vesicles and thereby carrying proteins to the base of the photoreceptor connecting cilium for transport to the outer segment [31]. RP1 encodes a photoreceptor – specific, microtubule associated ciliary protein, localized to the axoneme of outer segments (OS) and connecting cilia in rods. It plays a role in affecting photosensitivity and OS morphogenesis of rods [32].

Proteostasis. Misfolding of several proteins involved into retinal survival and vision process, like rhodopsin, can result in disruptions of cellular protein homeostasis (Proteostasis) [33]. Probably the interaction between several chaperones could be altered by oxidant agents, due to activation/deactivation switches that induce certain chaperones – encoding genes, like C1GALT1 Specific Chaperone 1 (*C1GALT1C1*) [34] and Ubiquitin Conjugating Enzyme E2 T (*UBE2T*) [35], or co – chaperones, like SGT1 Homolog, MIS12 Kinetochore Complex Assembly Cochaperone (*SUGT1*) [36], and repress other ones, like Apolipoprotein E (*APOE*) [37].

Signal transduction. Most inherited forms of blindness are caused by mutations that lead to photoreceptors death, but little is known of second – and third – order retinal neurons involvement. Expression of the light – gated excitatory mammalian ion channel light – gated ionotropic glutamate receptor (LiGluR) in retinal ganglion cells (RGCs) of the retina degeneration (rd1) mouse model of blindness was previously shown to restore some visual functions when stimulated by UV light [38]. Small guanosine triphosphate (GTPase) ADP – rybosilation factors

(Arfs) regulate membrane traffic and actin reorganization under the control of GTPase – activating proteins (GAPs) [39]. The constitutive isoform of RPGR, which is prenylated, requires prenylation for its ciliary localization. Ablation of phosphodiesterase 6 (PDE6D, for which RPGR acts as a scaffold protein to recruit cargo – loaded PDE6D to primary cilia) blocks ciliary targeting or RPGR [40].

Phototransduction. Mutations in particular genes encoding proteins involved in phototransduction cascades or visual cycle could impair rods functions, but ultimately affect both types of photoreceptors [41]. The beta – V spectrins homers couple some USH1 proteins, opsin and other phototransduction proteins to both actin – and microtubule – based motors, thereby contributing to their transport towards the photoreceptor outer disks [42]. Mutations in the membrane frizzled – related protein (MFRP/ Mftp) gene, specifically expressed in the RPE and ciliary body, determine a sensible reduction in expression of genes involved in visual cycle and phototransduction [43].

Neuron. RPE cells play a pivotal role in organizing the spatial structure of the retina, probably with a constant set of involved genes. A differentially regulated gene network in mouse models of RP could be fundamental to discover the mechanisms involved in neurite outgrowth and synaptic plasticity in altered retina [44]. Rods and cones in the RP maculas did not form neurites, but the axons of peripheral cones were abnormally elongated and branched [45]. Blocking gamma-aminobutyric acid c (GABAc) receptors increases light responsiveness of retinal ganglion cells in a rat model of RP [46].

Splicing. Retina cells express unusually high amounts of spliceosome components, which indicates a high demand for splicing [47]. Moreover, inefficient splicing and alterations in alternative splicing have been reported in cell culture experiments, animal models and blood cells derived from RP patients [48].

Endoplasmic Reticulum Stress and Unfolded Protein Response. Endoplasmic reticulum (ER) stress and Unfolded Protein Response (UPR) signaling have been implicated in the etiopathogenesis of heritable forms of retinitis pigmentosa [49]. UPR determines an initial inhibition of translation to prevent further accumulation of misfolded proteins, and an up – regulation of chaperones genes to improve protein folding, followed by activation of the ER – associated degradation system, which retro – translocates misfolded proteins from the ER for proteasome – dependent degradation. If ER stress persists, UPR signaling "switches" to trigger cell death by activating the intrinsic apoptosis pathway [50]. Particularly, Activating Transcription Factor 6 (*ATF6*), Bardet-Biedl Syndrome 10 (*BBS10*) and Top 1 Binding Arginine/Serine Rich Protein (*TOPORS1*) encode for proteins involved in response to misfolded proteins [51-55]. The UPR response in RPE cells is also activated by accumulation of mutant EGF Containing Fibulin Like Extracellular Matrix Protein 1 (EFEMP1), which should involve wolframin, an ER protein encoded by Wolframin ER Transmembrane Glycoprotein (*WFS1*) gene [56]. A new intriguing gene, involved in poly – ubiquitinating target proteins for proteasome – mediated degradation, is Kelch Like Family Member 7 (*KLHL7*). Mutations in *KLHL7* have recently been reported as causative of an autosomal – dominant form of retinitis pigmentosa (RP42), preferentially affecting the rod photoreceptors [57]. Patients with mutations in *KLHL7* showed thinner – than – normal RPE [58].

Specific transcription factor regulative network. Two transcription factors encoding genes linked to RP development, Zinc Finger Protein 513 (*ZNF513*) and Nuclear Receptor Subfamily 2 Group F Member 1 (*NR2F1*), resulted down – regulated in our experiment. Znf513 regulates expression of genes involved in retinal development and photoreceptor maintenance [59]. NR2F1, together with NR2F2, promotes optic vesicle development [60] and regulates lipid homeostasis under stress condition [61].

Extracellular matrix (ECM) remodeling. Two genes, TIMP Metallopeptidase Inhibitor 3 (*TIMP3*) and Collagen Type XI Alpha 1 Chain (*COL11A1*), encodes for proteins synthesized in RPE and then secreted in BM. Advanced glycation end – products (AGEs) and confluent drusen accumulate in BM, resulting in an uncontrolled activation of the complement cascade with onset of RP symptoms [62]. *TIMP3* encodes for an inhibitor of matrix metalloproteinases (MMPs). The balance between proteolytic MMPs and TIMPs underlies

the ECM remodeling. An increase of *TIMP3* mRNA expression in retinas affected by simplex RP is documented [63]. The ECM – involved *COL11A1* resulted, also, modified in its expression. Col11a1a is detectable in the RPE [64]. Although over – expression of ECM and pro – fibrotic proteins, like col11a1, is not yet related to specific form of RP, it was reported in primary open angle glaucoma (POAG) cells, compared with normal Gliar fibrillary acidic protein (GFAP)-negative lamina cribrosa (LC) cells [65]. The up – regulation of *TIMP3* and *COL11A1* could determine retinal cells apoptosis.

Cellular cycle regulation. In RPE, among several genes involved in cell cycle progression, Polo like kinase 4 (*PLK4*), Kinesin family member 11 (*KIF11*), Ceramide kinase like (*CERKL*) and RB1 inducible coiled-coil 1 (*RB1CC1*) resulted over - expressed after oxLDL treatment. Mutations in the PLK4 kinase determine microcephalic primordial dwarfism with additional congenital anomalies including retinopathy. The retinal pathology may result from perturbed mitosis in the eye, or as a consequence of impaired cilia formation leading to photoreceptor death [66]. Also mutations in the mitotic spindle binding motor kinesin KIF11 cause microcephaly and retinopathy [67]. CERKL and RB1CC1, instead, regulate the phagocytosis of outer segments (OSs) by the RPE [68, 69].

Phagocytosis and melanosomes transport in RPE. Photoreceptors maintain specific structure and dimensions by continuously renewal of outer segments, while simultaneously old and waste outer segments are phagocytized by the RPE. Perturbations in OS digestion can lead to retinopathies [70]. Myosin VIIA (*MYO7A*) encodes for the unconventional Myosin – VIIa, whose mutations cause Usher syndrome type 1B, a disorder involving profound congenital deafness and progressive blindness [71]. In the retina, most of MYO7A is localized in the apical region of the RPE cells, where participates in the localization of RPE melanosomes and in the delivery of phagosomes to lysosomes in the basal RPE. An additional role of MYO7A in the RPE is suggested by its requirement for light – dependent translocation of the ER – associated visual cycle enzyme, RPE65, and normal visual retinoid cycle physiology [72].

Retinoic acid cycle: Some RP cases are caused by an impaired retinoid cycle [73]. Several enzymes belonging to Retinal Deidrogenases (RDHs) family take part to visual cycle. RDH5 is very abundant in the RPE, where it is able to oxidize or to reduce all common cis – retinoid isomers [74]. Moreover, mevalonate kinase gene (*MVK*) results down – regulated in the same condition. MVK is involved in the isoprenoid pathway resulting in biosynthesis of glycoproteins, coenzyme Q, vitamin K and carotenoids (retinol biosynthesis). Furthermore, RP was described in several patients with MKV mutations [75].

References

1. Muniz A BB, Trevino AR, Buddavarapu K, Roman R, Ma JX, Tsin AT. Evidence for two retinoid cycles in the cone-dominated chicken eye. Biochemistry 2009;48:6854-63.
2. PA C. Molecular pathogenesis of retinal and choroidal vascular diseases. Prog Retin Eye Res 2015;49:67-81.
3. Nguyen-Legros J HD. Renewal of photoreceptor outer segments and their phagocytosis by the retinal pigment epithelium. Int Rev Cytol 2000;196:245-313.
4. King GL SK. Pigment-epithelium-derived factor--a key coordinator of retinal neuronal and vascular functions. N Engl J Med 2000;342:349-51.
5. Beatty S MI, Henson DB, Carden D, Koh H, Boulton ME. Macular pigment and risk for age-related macular degeneration in subjects from a Northern European population. Invest Ophthalmol Vis Sci 2001;42:439-46.
6. Daiger SP, Sullivan LS, Bowne SJ. Genes and mutations causing retinitis pigmentosa. Clin Genet 2013;84:132-41.
7. Patel N, Aldahmesh MA, Alkuraya H, Anazi S, Alsharif H, Khan AO, Sunker A, Al-Mohsen S, Abboud EB, Nowilaty SR, Alowain M, Al-Zaidan H, Al-Saud B, Alasmari A, Abdel-Salam GM, Abouelhoda M, Abdulwahab FM, Ibrahim N, Naim E, Al-Younes B, A EA, Allssa A, Hashem M, Buzovetsky O, Xiong Y, Monies D, Altassan N, Shaheen R, Al-Hazzaa SA, Alkuraya FS. Expanding the clinical, allelic, and locus heterogeneity of retinal dystrophies. Genet Med 2016;18:554-62.
8. Brandstetter C, Patt J, Holz FG, Krohne TU. Inflammasome priming increases retinal pigment epithelial cell susceptibility to lipofuscin phototoxicity by changing the cell death mechanism from apoptosis to pyroptosis. J Photochem Photobiol B 2016;161:177-83.

9. Dick AD. Doyne lecture 2016: intraocular health and the many faces of inflammation. Eye (Lond) 2017;31:87-96.
10. Liu Y, Zhou J, Wang L, Hu X, Liu X, Liu M, Cao Z, Shangguan D, Tan W. A Cyanine Dye to Probe Mitophagy: Simultaneous Detection of Mitochondria and Autolysosomes in Live Cells. J Am Chem Soc 2016;138:12368-74.
11. Rohrer B, Bandyopadhyay M, Beeson C. Reduced Metabolic Capacity in Aged Primary Retinal Pigment Epithelium (RPE) is Correlated with Increased Susceptibility to Oxidative Stress. Adv Exp Med Biol 2016;854:793-8.
12. Matsunaga D, Sreekumar PG, Ishikawa K, Terasaki H, Barron E, Cohen P, Kannan R, Hinton DR. Humanin Protects RPE Cells from Endoplasmic Reticulum Stress-Induced Apoptosis by Upregulation of Mitochondrial Glutathione. PLoS One 2016;11:e0165150.
13. Chichagova V, Hallam D, Collin J, Buskin A, Saretzki G, Armstrong L, Yu-Wai-Man P, Lako M, Steel DH. Human iPSC disease modelling reveals functional and structural defects in retinal pigment epithelial cells harbouring the m.3243A > G mitochondrial DNA mutation. Sci Rep 2017;7:12320.
14. Pinelli M, Carissimo A, Cutillo L, Lai CH, Mutarelli M, Moretti MN, Singh MV, Karali M, Carrella D, Pizzo M, Russo F, Ferrari S, Ponzin D, Angelini C, Banfi S, di Bernardo D. An atlas of gene expression and gene co-regulation in the human retina. Nucleic Acids Res 2016;44:5773-84.
15. Schmidt-Kastner R, Yamamoto H, Hamasaki D, Yamamoto H, Parel JM, Schmitz C, Dorey CK, Blanks JC, Preising MN. Hypoxia-regulated components of the U4/U6.U5 tri-small nuclear riboprotein complex: possible role in autosomal dominant retinitis pigmentosa. Mol Vis 2008;14:125-35.
16. Besharse JC, McMahon DG. The Retina and Other Light-sensitive Ocular Clocks. J Biol Rhythms 2016;31:223-43.
17. Sethna S, Chamakkala T, Gu X, Thompson TC, Cao G, Elliott MH, Finnemann SC. Regulation of Phagolysosomal Digestion by Caveolin-1 of the Retinal Pigment Epithelium Is Essential for Vision. J Biol Chem 2016;291:6494-506.
18. Fanjul-Moles ML, Lopez-Riquelme GO. Relationship between Oxidative Stress, Circadian Rhythms, and AMD. Oxid Med Cell Longev 2016;2016:7420637.
19. Yao J, Jia L, Shelby SJ, Ganios AM, Feathers K, Thompson DA, Zacks DN. Circadian and non-circadian modulation of autophagy in photoreceptors and retinal pigment epithelium. Invest Ophthalmol Vis Sci 2014;55:3237-46.
20. Olchawa MM, Furso JA, Szewczyk GM, Sarna TJ. Lipofuscin-mediated photic stress inhibits phagocytic activity of ARPE-19 cells; effect of donors' age and antioxidants. Free Radic Res 2017:1-13.
21. Laurent V, Sengupta A, Sanchez-Bretano A, Hicks D, Tosini G. Melatonin signaling affects the timing in the daily rhythm of phagocytic activity by the retinal pigment epithelium. Exp Eye Res 2017;165:90-95.
22. Hunter A, Spechler PA, Cwanger A, Song Y, Zhang Z, Ying GS, Hunter AK, Dezoeten E, Dunaief JL. DNA methylation is associated with altered gene expression in AMD. Invest Ophthalmol Vis Sci 2012;53:2089-105.
23. Alivand MR, Soheili ZS, Pornour M, Solali S, Sabouni F. Novel Epigenetic Controlling of Hypoxia Pathway Related to Overexpression and Promoter Hypomethylation of TET1 and TET2 in RPE Cells. J Cell Biochem 2017;118:3193-3204.
24. Amram B, Cohen-Tayar Y, David A, Ashery-Padan R. The retinal pigmented epithelium - from basic developmental biology research to translational approaches. Int J Dev Biol 2017;61:225-234.
25. Gong Y, Fu Z, Liegl R, Chen J, Hellstrom A, Smith LE. omega-3 and omega-6 long-chain PUFAs and their enzymatic metabolites in neovascular eye diseases. Am J Clin Nutr 2017;106:16-26.
26. Rice DS, Calandria JM, Gordon WC, Jun B, Zhou Y, Gelfman CM, Li S, Jin M, Knott EJ, Chang B, Abuin A, Issa T, Potter D, Platt KA, Bazan NG. Adiponectin receptor 1 conserves docosahexaenoic acid and promotes photoreceptor cell survival. Nat Commun 2015;6:6228.
27. Gorusupudi A, Liu A, Hageman GS, Bernstein PS. Associations of human retinal very long-chain polyunsaturated fatty acids with dietary lipid biomarkers. J Lipid Res 2016;57:499-508.
28. Azadi S, Brush RS, Anderson RE, Rajala RV. Class I Phosphoinositide 3-Kinase Exerts a Differential Role on Cell Survival and Cell Trafficking in Retina. Adv Exp Med Biol 2016;854:363-9.
29. Dutta N, Seo S. RPGR, a prenylated retinal ciliopathy protein, is targeted to cilia in a pre-

nylation- and PDE6D-dependent manner. Biol Open 2016;5:1283-9.
30. Di Gioia SA, Farinelli P, Letteboer SJ, Arsenijevic Y, Sharon D, Roepman R, Rivolta C. Interactome analysis reveals that FAM161A, deficient in recessive retinitis pigmentosa, is a component of the Golgi-centrosomal network. Hum Mol Genet 2015;24:3359-71.
31. Schwarz N, Lane A, Jovanovic K, Parfitt DA, Aguila M, Thompson CL, da Cruz L, Coffey PJ, Chapple JP, Hardcastle AJ, Cheetham ME. Arl3 and RP2 regulate the trafficking of ciliary tip kinesins. Hum Mol Genet 2017;26:2480-2492.
32. Kabir F, Ullah I, Ali S, Gottsch AD, Naeem MA, Assir MZ, Khan SN, Akram J, Riazuddin S, Ayyagari R, Hejtmancik JF, Riazuddin SA. Loss of function mutations in RP1 are responsible for retinitis pigmentosa in consanguineous familial cases. Mol Vis 2016;22:610-25.
33. Lin JH, Lavail MM. Misfolded proteins and retinal dystrophies. Adv Exp Med Biol 2010;664:115-21.
34. Xie LS, Qin W, Fan JM, Huang J, Xie XS, Li Z. The role of C1GALT1C1 in lipopolysaccharide-induced IgA1 aberrant O-glycosylation in IgA nephropathy. Clin Invest Med 2010;33:E5-13.
35. Alpi AF, Chaugule V, Walden H. Mechanism and disease association of E2-conjugating enzymes: lessons from UBE2T and UBE2L3. Biochem J 2016;473:3401-3419.
36. Niikura Y, Kitagawa R, Ogi H, Kitagawa K. SGT1-HSP90 complex is required for CENP-A deposition at centromeres. Cell Cycle 2017;16:1683-1694.
37. Yang P, Skiba NP, Tewkesbury GM, Treboschi VM, Baciu P, Jaffe GJ. Complement-Mediated Regulation of Apolipoprotein E in Cultured Human RPE Cells. Invest Ophthalmol Vis Sci 2017;58:3073-3085.
38. Gaub BM, Berry MH, Holt AE, Reiner A, Kienzler MA, Dolgova N, Nikonov S, Aguirre GD, Beltran WA, Flannery JG, Isacoff EY. Restoration of visual function by expression of a light-gated mammalian ion channel in retinal ganglion cells or ON-bipolar cells. Proc Natl Acad Sci U S A 2014;111:E5574-83.
39. Luo R, Reed CE, Sload JA, Wordeman L, Randazzo PA, Chen PW. Arf GAPs and molecular motors. Small GTPases 2017:1-14.
40. Lee JJ, Seo S. PDE6D binds to the C-terminus of RPGR in a prenylation-dependent manner. EMBO Rep 2015;16:1581-2.
41. Nash BM, Wright DC, Grigg JR, Bennetts B, Jamieson RV. Retinal dystrophies, genomic applications in diagnosis and prospects for therapy. Transl Pediatr 2015;4:139-63.
42. Papal S, Cortese M, Legendre K, Sorusch N, Dragavon J, Sahly I, Shorte S, Wolfrum U, Petit C, El-Amraoui A. The giant spectrin betaV couples the molecular motors to phototransduction and Usher syndrome type I proteins along their trafficking route. Hum Mol Genet 2013;22:3773-88.
43. Fogerty J, Besharse JC. 174delG mutation in mouse MFRP causes photoreceptor degeneration and RPE atrophy. Invest Ophthalmol Vis Sci 2011;52:7256-66.
44. Sugitani K, Koriyama Y, Ogai K, Wakasugi K, Kato S. A Possible Role of Neuroglobin in the Retina After Optic Nerve Injury: A Comparative Study of Zebrafish and Mouse Retina. Adv Exp Med Biol 2016;854:671-5.
45. Li ZY, Kljavin IJ, Milam AH. Rod photoreceptor neurite sprouting in retinitis pigmentosa. J Neurosci 1995;15:5429-38.
46. Jensen RJ. Blocking GABA(C) receptors increases light responsiveness of retinal ganglion cells in a rat model of retinitis pigmentosa. Exp Eye Res 2012;105:21-6.
47. Karunakaran DK, Al Seesi S, Banday AR, Baumgartner M, Olthof A, Lemoine C, Mandoiu, II, Kanadia RN. Network-based bioinformatics analysis of spatio-temporal RNA-Seq data reveals transcriptional programs underpinning normal and aberrant retinal development. BMC Genomics 2016;17 Suppl 5:495.
48. Tanackovic G, Ransijn A, Thibault P, Abou Elela S, Klinck R, Berson EL, Chabot B, Rivolta C. PRPF mutations are associated with generalized defects in spliceosome formation and pre-mRNA splicing in patients with retinitis pigmentosa. Hum Mol Genet 2011;20:2116-30.
49. Shinde V, Kotla P, Strang C, Gorbatyuk M. Unfolded protein response-induced dysregulation of calcium homeostasis promotes retinal degeneration in rat models of autosomal dominant retinitis pigmentosa. Cell Death Dis 2016;7:e2085.
50. Hiramatsu N, Chiang WC, Kurt TD, Sigurdson CJ, Lin JH. Multiple Mechanisms of Unfolded Protein Response-Induced Cell Death. Am J Pathol 2015;185:1800-8.
51. Esposito G, Testa F, Zacchia M, Crispo AA, Di

Iorio V, Capolongo G, Rinaldi L, D'Antonio M, Fioretti T, Iadicicco P, Rossi S, Franze A, Marciano E, Capasso G, Simonelli F, Salvatore F. Genetic characterization of Italian patients with Bardet-Biedl syndrome and correlation to ocular, renal and audio-vestibular phenotype: identification of eleven novel pathogenic sequence variants. BMC Med Genet 2017;18:10.
52. Farkas MH, Lew DS, Sousa ME, Bujakowska K, Chatagnon J, Bhattacharya SS, Pierce EA, Nandrot EF. Mutations in pre-mRNA processing factors 3, 8, and 31 cause dysfunction of the retinal pigment epithelium. Am J Pathol 2014;184:2641-52.
53. Jerry Chiang WC, Lin JH. The effects of IRE1, ATF6, and PERK signaling on adRP-linked rhodopsins. Adv Exp Med Biol 2014;801:661-7.
54. Ruzickova S, Stanek D. Mutations in spliceosomal proteins and retina degeneration. RNA Biol 2017;14:544-552.
55. Yoshikawa T, Ogata N, Izuta H, Shimazawa M, Hara H, Takahashi K. Increased expression of tight junctions in ARPE-19 cells under endoplasmic reticulum stress. Curr Eye Res 2011;36:1153-63.
56. Schmidt-Kastner R, Kreczmanski P, Preising M, Diederen R, Schmitz C, Reis D, Blanks J, Dorey CK. Expression of the diabetes risk gene wolframin (WFS1) in the human retina. Exp Eye Res 2009;89:568-74.
57. Angius A, Uva P, Buers I, Oppo M, Puddu A, Onano S, Persico I, Loi A, Marcia L, Hohne W, Cuccuru G, Fotia G, Deiana M, Marongiu M, Atalay HT, Inan S, El Assy O, Smit LM, Okur I, Boduroglu K, Utine GE, Kilic E, Zampino G, Crisponi G, Crisponi L, Rutsch F. Bi-allelic Mutations in KLHL7 Cause a Crisponi/CISS1-like Phenotype Associated with Early-Onset Retinitis Pigmentosa. Am J Hum Genet 2016;99:236-45.
58. Wen Y, Locke KG, Klein M, Bowne SJ, Sullivan LS, Ray JW, Daiger SP, Birch DG, Hughbanks-Wheaton DK. Phenotypic characterization of 3 families with autosomal dominant retinitis pigmentosa due to mutations in KLHL7. Arch Ophthalmol 2011;129:1475-82.
59. Li L, Nakaya N, Chavali VR, Ma Z, Jiao X, Sieving PA, Riazuddin S, Tomarev SI, Ayyagari R, Riazuddin SA, Hejtmancik JF. A mutation in ZNF513, a putative regulator of photoreceptor development, causes autosomal-recessive retinitis pigmentosa. Am J Hum Genet 2010;87:400-9.
60. Tang K, Xie X, Park JI, Jamrich M, Tsai S, Tsai MJ. COUP-TFs regulate eye development by controlling factors essential for optic vesicle morphogenesis. Development 2010;137:725-34.
61. Cho KI, Yi H, Tserentsoodol N, Searle K, Ferreira PA. Neuroprotection resulting from insufficiency of RANBP2 is associated with the modulation of protein and lipid homeostasis of functionally diverse but linked pathways in response to oxidative stress. Dis Model Mech 2010;3:595-604.
62. Booij JC, Baas DC, Beisekeeva J, Gorgels TG, Bergen AA. The dynamic nature of Bruch's membrane. Prog Retin Eye Res 2010;29:1-18.
63. Jomary C, Neal MJ, Jones SE. Increased expression of retinal TIMP3 mRNA in simplex retinitis pigmentosa is localized to photoreceptor-retaining regions. J Neurochem 1995;64:2370-3.
64. Fang M, Adams JS, McMahan BL, Brown RJ, Oxford JT. The expression patterns of minor fibrillar collagens during development in zebrafish. Gene Expr Patterns 2010;10:315-22.
65. Kirwan RP, Wordinger RJ, Clark AF, O'Brien CJ. Differential global and extra-cellular matrix focused gene expression patterns between normal and glaucomatous human lamina cribrosa cells. Mol Vis 2009;15:76-88.
66. Martin CA, Ahmad I, Klingseisen A, Hussain MS, Bicknell LS, Leitch A, Nurnberg G, Toliat MR, Murray JE, Hunt D, Khan F, Ali Z, Tinschert S, Ding J, Keith C, Harley ME, Heyn P, Muller R, Hoffmann I, Cormier-Daire V, Dollfus H, Dupuis L, Bashamboo A, McElreavey K, Kariminejad A, Mendoza-Londono R, Moore AT, Saggar A, Schlechter C, Weleber R, Thiele H, Altmuller J, Hohne W, Hurles ME, Noegel AA, Baig SM, Nurnberg P, Jackson AP. Mutations in PLK4, encoding a master regulator of centriole biogenesis, cause microcephaly, growth failure and retinopathy. Nat Genet 2014;46:1283-1292.
67. Choi SH, McCollum D. A role for metaphase spindle elongation forces in correction of merotelic kinetochore attachments. Curr Biol 2012;22:225-30.
68. Yao J, Jia L, Khan N, Lin C, Mitter SK, Boulton ME, Dunaief JL, Klionsky DJ, Guan JL, Thompson DA, Zacks DN. Deletion of autophagy inducer RB1CC1 results in degeneration of

the retinal pigment epithelium. Autophagy 2015;11:939-53.
69. Yu S, Li C, Biswas L, Hu X, Liu F, Reilly J, Liu X, Liu Y, Huang Y, Lu Z, Han S, Wang L, Yu Liu J, Jiang T, Shu X, Wong F, Tang Z, Liu M. CERKL gene knockout disturbs photoreceptor outer segment phagocytosis and causes rod-cone dystrophy in zebrafish. Hum Mol Genet 2017;26:2335-2345.
70. Kevany BM, Palczewski K. Phagocytosis of retinal rod and cone photoreceptors. Physiology (Bethesda) 2010;25:8-15.
71. Xia H, Hu P, Yuan L, Xiong W, Xu H, Yi J, Yang Z, Deng X, Guo Y, Deng H. A homozygous MYO7A mutation associated to Usher syndrome and unilateral auditory neuropathy spectrum disorder. Mol Med Rep 2017;16:4241-4246.
72. Williams DS, Lopes VS. The many different cellular functions of MYO7A in the retina. Biochem Soc Trans 2011;39:1207-10.
73. Travis GH, Golczak M, Moise AR, Palczewski K. Diseases caused by defects in the visual cycle: retinoids as potential therapeutic agents. Annu Rev Pharmacol Toxicol 2007;47:469-512.
74. Parker RO, Crouch RK. Retinol dehydrogenases (RDHs) in the visual cycle. Exp Eye Res 2010;91:788-92.
75. Siemiatkowska AM, van den Born LI, van Hagen PM, Stoffels M, Neveling K, Henkes A, Kipping-Geertsema M, Hoefsloot LH, Hoyng CB, Simon A, den Hollander AI, Cremers FP, Collin RW. Mutations in the mevalonate kinase (MVK) gene cause nonsyndromic retinitis pigmentosa. Ophthalmology 2013;120:2697-705.