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The versatile roles of retinal pigment epithelium in the pathophysiology of retinitis pigmentosa

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ABSTRACT

Retinitis pigmentosa (RP) is a group of hereditary retinal diseases that lead to progressive vision loss, with most disease-causing genes expressed in rod photoreceptors and a smaller fraction in retinal pigment epithelium (RPE) cells. The RPE and photoreceptor cells share a symbiotic relationship characterized by close spatial and functional interactions that play a pivotal role in vision. Although the role of RPE is fundamental to the retina, its involvement in retinal pathogenesis, and, in particular, in RP remains underappreciated. In this review, we summarize morphological alterations in the RPE resulting from pathogenic mutations specific to RPE cells, as well as those occurring secondary to photoreceptor degeneration. We provide a comprehensive summary of how mutations in RPE-specific genes play a key role in the pathophysiology of RP. Finally, we discuss the latest therapeutic approaches, including AAV-mediated gene augmentation, RPE cell transplantation, and pharmacological interventions.

1. Introduction

The complexity of the vertebrate eye is underpinned by its cellular heterogeneity and the interconnectivity between cells that allows the establishment of functional synergetic circuits to produce visual output. This is particularly reflected by the high level of cooperation and interdependence between the retinal pigment epithelium (RPE) and the photoreceptors, rendering both cell types into one functional unit. The RPE provides essential support for photoreceptor function and integrity, including maintenance of the visual cycle (Tsin et al., 2018), phagocytosis of photoreceptor outer segments (Kwon and Freeman, 2020), the establishment of a physical barrier (Cunha-Vaz et al., 2011), and delivery of nutrients (Kanow et al., 2017).

While the symbiotic relationship between the RPE and photoreceptors effectively enables the complex phototransduction process, it is also prone to dysfunctions, as alterations in one cell type can affect the other. This becomes evident in diseases like retinitis pigmentosa (RP), the most common cause of inherited blindness (Hartong et al., 2006; Karuntu et al., 2024). To date, mutations in over 119 genes have been identified to cause RP (Stone et al., 2017; Pontikos et al., 2020; Tracewska et al., 2021), and in most cases, the disease-causing gene is exclusively expressed in rods. The initial mutation-driven rod photoreceptor degeneration leads to the secondary death of neighboring cone photoreceptors (John et al., 2000; McGuigan et al., 2017; Song et al., 2023) and RPE remodeling (Li et al., 1995; Jones et al., 2016).

While there exists a substantial literature on the role of RPE in age-related macular degeneration (AMD) and diabetic retinopathies (Xu et al., 2011; Somasundaran et al., 2020), relatively few studies have focused on how RPE alterations contribute to RP pathogenesis (Napoli et al., 2021; Napoli and Strettoi, 2023; Peng et al., 2024). In this review, we describe our current knowledge of the structural alterations of RPE cells in RP patients and mouse models. We review the contributions of dysfunctional RPE cells in RP pathogenesis, including defects in the visual cycle, phagocytosis, and altered metabolic support. Last, we discuss the potential of the RPE as a therapeutic target for RP.

2. Retinitis pigmentosa (RP)

RP encompasses a group of inherited retinal dystrophies that result in a gradual loss of visual function. The conservative prevalence of RP is estimated to be 1 in 5000 worldwide, making it the most common hereditary cause of retinal degeneration. At the cellular level, the primary degeneration of the rod photoreceptors is followed by secondary loss of cones as the disease progresses (Newton and Megaw, 2020). Rods make up 95 % of human photoreceptors and are responsible for vision in dim light (scotopic vision). Cones, which are densely packed in the center of

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the human retina, mediate color and high-acuity vision (photopic vision) (Lamb, 2016). This general pattern of rod-cone degeneration explains why the disease initially manifests as night blindness (nyctalopia), followed by progressive visual field constriction and, ultimately, loss of central vision at the onset of cone degeneration. Thus, in late disease stages, patients experience a partial or complete loss of diurnal vision (Berson et al., 2002; Bennett et al., 2020; Kim et al., 2020), and some eventually progress to blindness (Di Iorio et al., 2020; Lisbjerg et al., 2023b; Xu et al., 2020). As photoreceptors undergo cell death, an abnormal fundus with bone spicule pigmentation can be observed due to the migration of RPE cells into the neural retina. Additional clinical hallmarks include attenuated retinal vessels and a waxy pallor of the optic nerve head (Natarajan 2011).

RP is a highly genetically heterogeneous disease, with more than 3000 mutations in over 119 genes identified to date (Stone et al., 2017; Pontikos et al., 2020; Tracewska et al., 2021) (Table 1). Additionally, there is a wide phenotypic variability, where the clinical presentation, onset, severity, and rate of disease progression vary depending on the causative gene and inheritance pattern. Approximately 50–60 % of RP cases are autosomal recessive, 30–40 % are autosomal dominant, and 10 % are X-linked recessive (Verbakel et al., 2018). Autosomal dominant RP cases have been associated with incomplete penetrance (McGee et al., 1997; Rose et al., 2016), with some carriers being clinically asymptomatic (Lisbjerg et al., 2023a). The conspicuous variation between individuals with RP may also be related to demographic factors (such as ethnicity, age, sex, educational and socioeconomic level), smoking (Huang et al., 2022), physical activity, diet (Huang et al., 2022), and modifier genes (Baz-Redón et al., 2024). Additionally, the same mutation can have a spectrum of outcomes and clinical manifestations, even within members of the same family (Daiger et al., 2013). Such genetic complexity and genotype-phenotype variability can cause prognostic delays and mistakes for patients. To add up, there is a clinical overlap between RP and Leber congenital amaurosis (LCA), an early-onset retinal degenerative disease, with shared genes and pathogenesis (Cremers et al., 1998; Morimura et al., 1998; den Hollander et al., 2001). While most of these pathogenic genes are rod-specific, mutations in genes expressed in the RPE can also lead to photoreceptor degeneration, highlighting the intertwined relationship between the two cell types. The disease-causing genes map into different key biological pathways, including the phototransduction cascade and visual cycle (McLaughlin et al., 1995; Illing et al., 2002), ciliary function (Nishiguchi et al., 2013; Xu et al., 2015; Goyal et al., 2016), and pathways involved in maintaining the structural integrity of the RPE and photoreceptors (Bandah-Rozenfeld et al., 2010; Bujakowska et al., 2015), Additionally, many disease-causing genes are associated with general processes such as signal transduction (Corton et al., 2016), lysosome homeostasis (Jin et al., 2014; Haer-Wigman et al., 2015; De Geer et al., 2023), cytoskeleton function (Wada et al., 2001; Khan et al., 2011; Kastner et al., 2015) and RNA processing/homeostasis (Bujakowska et al., 2009; Benaglio et al., 2011; Ajmal et al., 2014). Contributory pathophysiological mechanisms are summarized in Fig. 1 and in Table 1. Causative genes are listed in Table 1.

3. Structural features of healthy RPE cells

The RPE is a cellular monolayer comprised of tightly arranged pigmented hexanocuboidal epithelial cells juxtaposed between the photoreceptors and the choroidal vasculature. Like other epithelial tissues, the structural hallmarks of RPE cells are the presence of tight junctions between adjacent cells and their apical-basal polarization. This structure of RPE cells adapts to highly spatiotemporally regulated mechanisms essential for retinal homeostasis, such as phagocytosis, phototransduction, barrier, and transport of nutrients, water, and oxygen (Strauss, 2005). Therefore, understanding the structure and organization of healthy RPE cells is crucial for identifying phenotypic changes in the RPE associated with RP. Additionally, gaining a better

Table 1
List of genes, proteins, and their functions implicated in RP pathogenesis. Genes were clustered according to their biological processes.

Gene	Gene/Protein Name	Function
Phototransduction (8 genes)		
CNGA1	Cyclic Nucleotide-Gated Channel Alpha 1	Alpha subunit of cGMP-gated ion channel
CNGB1	Cyclic Nucleotide-Gated Channel Beta 1	Beta subunit of cGMP-gated ion channel
GUCA1B	Guanylate Cyclase Activator 1B	Activates guanylate cyclase (synthesis of cGMP)
PDE6A	Phosphodiesterase 6A	Catalytic subunit of rod PDE6 (hydrolysis of cGMP)
PDE6B	Phosphodiesterase 6B	Catalytic subunit of rod PDE6 (hydrolysis of cGMP)
PDE6G	Phosphodiesterase 6G	Inhibitory subunit of PE6 (hydrolysis of cGMP)
RHO	Rhodopsin	Light absorption
SAG	S-antigen (Visual Arrestin)	Rhodopsin inactivation
Inner and Outer Segments Morphogenesis (20 genes)		
AHI1	Abelson Helper Integration Site 1	Outer segment development
ARL2BP	ADP-Ribosylation Factor-Like 2 Binding Protein	Ciliary integrity
ARL6	ADP-Ribosylation Factor-Like 6	Outer segment organization
C8orf37/ CFAP418	Chromosome 8 Open Reading Frame 37/Cilia and Flagella Associated Protein 418	Ciliary maintenance and protein trafficking to the outer segment
CC2D2A	Coiled-Coil and C2 Containing 2A	Cilia formation
EYS	Eyes Shut Homolog	Outer segment organization
IFT43	Intraflagellar Transport 43	Ciliary transport complex component
IMPG2	Interphotoreceptor Matrix Proteoglycan-2	Interphotoreceptor matrix integrity
MAK	Male Germ-Cell Associated Kinase	Regulation of photoreceptor ciliary length
PCARE (C2orf71, RP54)	Photoreceptor Cilium Actin Regulator	Formation and maintenance of the photoreceptor outer segment
PRCD	Progressive Rod-Cone Degeneration	Outer segment development
PROM1	Prominin 1	Outer segment organization
PRPH2 (RDS)	Peripherin-2 (Retinal Degeneration Slow)	Outer segment organization
ROM1	Rod Outer Segment Membrane Protein 1	Outer segment organization
RP1	Retinitis Pigmentosa 1	Outer segment organization
RP1L1	Retinitis Pigmentosa 1-Like 1	Outer segment organization
RPGR	Retinitis Pigmentosa GTPase Regulator	Ciliary transport
TTC8	Tetratricopeptide Repeat Domain 8	Ciliary transport
USH2A	Usherin	Outer segment organization and ciliary transport
Epithelial cell junction formation and maintenance (3 genes)		
ARHGEF19	Rho Guanine Nucleotide Exchange Factor 19	Epithelial barrier integrity
CRB1	Crumbs Cell Polarity Complex Component 1	Epithelial barrier integrity
CRB2	Crumbs Cell Polarity Complex Component 2	Epithelial barrier integrity
Phagocytosis (1 gene)		

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Table 1 (*continued*)

Gene	Gene/Protein Name	Function
MERTK	MER proto-oncogene, Tyrosine Kinase	Phagocytosis
mRNA splicing (8 genes)		
CWC27	CWC27 Spliceosome-Associated Cyclophilin	mRNA splicing
DHX38	DEAH-Box Helicase 38	mRNA splicing
PRPF3	Pre-mRNA Processing Factor 3	mRNA splicing
PRPF4	Pre-mRNA Processing Factor 4	mRNA splicing
PRPF6	Pre-mRNA Processing Factor 6	mRNA splicing
PRPF8	Pre-mRNA Processing Factor 8	mRNA splicing
PRPF31	Pre-mRNA Processing Factor 31	mRNA splicing
RP9 (PAP1)	RP9 Pre-mRNA Splicing Factor	mRNA splicing
Visual cycle (7 genes)		
ABCA4	ATP Binding Cassette Subfamily A Member 4	Prevents the accumulation of toxic retinoid compounds
LRAT	Lecithin Retinol Acetyltransferase	Converts all-trans retinol to all-trans retinyl esters
RBP3	Retinol Binding Protein 3	Transports retinoids between RPE and photoreceptors
RDH12	Retinol Dehydrogenase 12	Converts all-trans-retinal to all-trans-retinol
RGR	Retinal G Protein-Coupled Receptor	Converts all-trans-retinal to 11-cis-retinal
RLBP1	Retinaldehyde-Binding Protein 1 (CRALBP)	Binds and transports 11-cis-retinal and 11-cis-retinol
RPE65	Retinal Pigment Epithelium-specific 65 kDa Protein	Converts all-trans-retinyl esters to 11-cis-retinol
Intracellular transport and traffic (4 genes)		
GNPTG	N-Acetylglucosamine-1-Phosphate Transferase Subunit Gamma	Tags lysosomal enzymes with mannose-6-phosphate (M6P) for proper delivery to lysosomes
KIF3B	Kinesin Family Member 3B	Intracellular transport
REEP6	Receptor Expression-Enhancing Protein 6	Involved in maintaining endoplasmic reticulum morphology and protein transport
SEMA4A	Semaphorin 4A	Endosomal sorting of the retinoid-binding proteins CRALBP and CRBP1
Metabolism (22 genes)		
ADIPOR1	Adiponectin Receptor 1	Uptake and retention of DHA
AHR	Aryl Hydrocarbon Receptor	Xenobiotic metabolism and detoxification
CERKL	CERamide Kinase Like	Mitochondria homeostasis
COQ2	Coenzyme Q2	Coenzyme Q biosynthesis pathway
COQ4 (COQ10D7, SPAX10)	Coenzyme Q4	Coenzyme Q biosynthesis pathway
COQ5	Coenzyme Q5	Coenzyme Q biosynthesis pathway
COQ8B (ADCK4, NPHS9)	Coenzyme Q8b	Coenzyme Q biosynthesis pathway
CYP4V2	Cytochrome P450 Family 4 Subfamily V Member 2	Fatty acid and lipid metabolism
DHDDS	Dehydrodolichyl Diphosphate Synthetase	Dolichol synthesis pathway
FLVCR1	Feline Leukemia Virus Subgroup C Receptor 1	Heme exporter
HGSNAT	Heparan-Alpha-Glucosaminide N-Acetyltransferase	Acetylates heparin and heparan sulfate in lysosomes
HK1	Hexokinase 1	Glycolysis
HKDC1 (RP92)	Hexokinase Domain Containing 1	Glucose metabolism
IDH3A	Isocitrate Dehydrogenase (NAD(+)) 3 Catalytic Subunit Alpha	TCA cycle
IDH3B	Isocitrate Dehydrogenase (NAD(+)) 3 Non-Catalytic Subunit Beta	TCA cycle
IMPDH1	Inosine Monophosphate Dehydrogenase 1	De novo guanine synthesis; DNA and RNA synthesis
MT-ATP6	Mitochondrially Encoded ATP Synthase Membrane Subunit 6	Part of the ATP synthase enzyme complex in the mitochondria
MVK	Mevalonate Kinase	Isoprenoid metabolism
PANK2 (HARP, PKAN)	Pantothenate Kinase 2	CoA biosynthesis
PDSS1 (COQ10D2)	Decaprenyl Diphosphate Synthase Subunit 1	Biosynthesis of coenzyme Q10
POMGNT1	Protein O-Linked Acetylglucosaminyltransferase 1 (Beta 1,2-)	O-mannosylation glycosylation
TTPA	Alpha Tocopherol Transfer Protein	Vitamin E metabolism
Ciliary transport (13 genes)		
ARL3	ARF like GTPase 3	Protein trafficking
BBS1	Bardet-Biedl Syndrome 1	Protein trafficking
BBS2	Bardet-Biedl Syndrome 2	Protein trafficking
IFT140	Intraflagellar Transport Complex 140	Mediates retrograde transport
IFT172 (NPHP17, RP71, SRTD10)	Intraflagellar Transport Complex 172	Correct localization of specific photoreceptor outer segment proteins
KIAA1549	KIAA1549	Formation and functioning of the synapse between photoreceptors and their postsynaptic cells
NEK2 (NLK1, RP67)	Nima Related Kinase 2	Trafficking of rhodopsin to the outer segments
RP2	RP2 Activator of ARL3 GTPase	Trafficking of lipidated proteins to the outer segments
SCAPER	S-Phase Cyclin A Associated Protein In The Endoplasmic Reticulum	Ciliary dynamics and disassembly
SPATA7	Spermatogenesis Associated 7	Maintenance of the connecting cilium
TBC1D32	TBC1 Domain Family Member 32	Ciliogenesis of the RPE
TMEM216	Transmembrane Protein 216	Primary ciliogenesis
TULP1 (LCA15, RP14)	Tubby-Like Gene Family	Protein transport between the inner and outer segments
Ion channels, transporters and regulators (7 genes)		
BEST1	Bestrophin-1	Chloride channel
CLCC1	Chloride Channel (CLIC) Like 1	Intracellular chloride channel
ENSA	Endosulfine Alpha	Regulates ion channel activity
SLC37A3	Solute Carrier Family 37 Member 3	Xenobiotic transmembrane transport
SLC39A12	Solute Carrier Family 39 Member 12	Zinc transport
SLC66A1	Solute Carrier Family 66 Member 1	pH-dependent export of the cationic amino acids arginine, histidine, and lysine from lysosomes
SLC7A14	Solute Carrier Family 7 Member 14	Mediates lysosomal uptake of arginine
Extracellular matrix and cytoskeleton (7 genes)		
AGBL5	AGBL Carboxypeptidase 5	Posttranslational modification of tubulin in microtubules
CLRN1	Clarin-1 Molecular Scaffold	Actin cytoskeleton organization

(*continued on next page*)

Table 1 (*continued*)

Gene	Gene/Protein Name	Function
FAM161A	Family with sequence similarity 161 member A	Centrosomal protein
FSCN2	Fascin Actin-Bundling Protein 2	Crosslinks actin into filamentous bundles, presumably for disk morphogenesis
IMPG1 (IPM150, RP91, SPARC, VDM4, BCAMD)	Interphotoreceptor Matrix Proteoglycan 1	Component of the extracellular matrix
KIZ	Kizuna Centrosomal Protein	Stabilizes centrosome
OFD1 (RP23)	Oral-Facial-Digital Syndrome 1	Centrosomal protein
Retinal development (8 genes)		
CRX	Cone-Rod Homeobox	Differentiation of photoreceptor
NEUROD1	Neuronal Differentiation Protein 1	Photoreceptor differentiation and survival
NR2E3	Nuclear Receptor Subfamily 2 Group E3	Transcriptional activator of rod-specific genes and repressor of cone-specific genes
NRL	Neural Retina Lucine Zipper	Transcription factor involved in rod photoreceptor specification
RAX2	Retina and Anterior Neural Fold Homeobox 2 Transcription Factor	Eye development
SAMD11	Sterile Alpha Motif Domain Containing 11 Protein	Signal transduction and transcription regulation
ZNF408	Zinc Finger Protein 408	Transcription factor
ZNF513	Zinc Finger Protein 513	Transcriptional repression of rhodopsin
Other/Unknown (11 genes)		
ADGRA3	Adhesion G Protein-Coupled Receptor A3	G protein-coupled receptor of unknown function
CA4	Carbonic Anhydrase IV	Regulation of pH homeostasis
EMC1	ER Membrane Protein Complex Subunit 1	Catalyzes the hydration of carbon dioxide
EXOSC2	Ribosomal RNA-Processing Protein 4' (RRP4)	Component of RNA exosome complex
MT-TS2	Mitochondrially Encoded tRNA Serine 2	Mitochondrial mRNA translation
PROS1	Protein S	Regulation of vascular permeability
RP17	Retinitis Pigmentosa-17	Structural variants associated with ectopic gene expression in the retina
SNRNP200	Small Nuclear Ribonucleoprotein U5 Subunit 200	Splice-complex protein
SPP2	Secreted Phosphoprotein 2	Secreted phosphoprotein of uncertain function
TRNT1	CCA Adding Trna Nucleotidyl Transferase 1	tRNA function and protein synthesis
VWA8 (RP97, P7BP2, KIAA0564)	Von Willebrand Factor A Domain Containing 8	Mitochondrial matrix-targeted protein

understanding of how disrupted polarity and junctional complexes contribute to retinal degeneration is essential.

Adjacent RPE cells are connected by tight junctions, composed of a complex network of transmembrane and peripheral cytoplasmic proteins. Transmembrane proteins include the occludins, the claudins, the MARVEL (Mal and related proteins for vesicle trafficking and membrane link) family, and junctional adhesion molecules (JAMs). Cytoplasmic proteins comprise zonula occludens-1 (ZO-1), −2 (ZO-2), and −3 (ZO-3). The integral transmembrane proteins occludins and claudins are responsible for the formation of a paracellular barrier to prevent diffusion of solutes between the choroidal vasculature and the neural retina (Rahner et al., 2004; Peng et al., 2011). The scaffolding protein ZO-1 is the most studied in RPE and is a major regulator of junctional complexes. It provides a high-quality outline of the RPE cell border that helps to demarcate the basal and apical membrane domains of RPE cells and, thus, their polarity (Martin et al., 2009; Jiang et al., 2013). ZO-1 also anchors junctional membrane proteins to the cytoskeleton components such as F-actin (Fanning et al., 2002; Georgiadis et al., 2010). Its disruption results in a loss of barrier function and cytoskeleton reorganization (Naylor et al., 2020).

The polarized architecture of the RPE is characterized by distinct cellular domains (Figs. 2 and 3). The basal side of the RPE resides on a permeable, acellular layer called the Bruch's membrane, which separates it from the choroid. The term basal labyrinth (Hayes et al., 2019) refers to the deep basal infoldings, an essential feature that increases surface area for nutrient and oxygen exchange. At the basolateral side, the tight junctions of RPE, together with the fenestrated endothelial cells of the choroid, form the outer blood-retinal barrier (BRB). The outer BRB allows the vectorial transport of oxygen, metabolites such as glucose, solutes, water, and other nutrients from the choroid to photoreceptors while removing harmful waste products from the retina. The monocarboxylate transporter MCT3 is distinctly localized to the basal side (Alm and Törnquist, 1985; Philp et al. 1998, 2001). Due to the high metabolic turnover of photoreceptors, large amounts of water and electrolytes are produced. They must be eliminated from the retina to the choriocapillaris, for instance, via ion channels such as bestrophin, an RPE-specific calcium-activated chloride channel (Marmorstein et al., 2000; Rosenthal et al., 2006; Hellinen et al., 2019). Another important function of the RPE is supporting the choroid vasculature by releasing angiogenic trophic factors at its basal domain, such as vascular endothelial growth factor-A (VEGF) (Blaauwgeers et al., 1999), endothelin-1 (Narayan et al., 2004), and galecin-1 (Wu et al., 2019).

On their apical side, the RPE cells are characterized by long, thin protrusions named microvilli that interdigitate the adjacent photoreceptor outer segments (Boulton and Dayhaw-Barker, 2001). This close spatial association is demonstrated in the immunohistochemical and high-resolution electron microscopy images presented in Fig. 2. There are two types of apical microvilli that serve specific functions. The long, thin microvilli are involved in trans-epithelial transport, and the cylindrical, short microvilli termed sheaths are the site of phagocytosis. Interestingly, RPE cells show a reversed polarity compared to other epithelial cells, an example of how RPE structure adapts to certain localization and function. Neural cell adhesion molecule (N-CAM), extracellular matrix metalloproteinase inducer (EMMPRIN), Na^+/K^+-ATPase, the lactate transporter MCT1, and the chloride channel protein 2 (CLC-2) exhibit an apically polarized localization (Marmorstein et al., 1998; Philp et al., 1998; Lobato-Álvarez et al., 2016; Hanke-Gogokhia et al., 2021). It has been postulated that CLC-2 (Hanke-Gogokhia et al., 2021), similar to Na^+/K^+-ATPase (Lobato-Álvarez et al., 2016), plays a key role in regulating and buffering the ion composition of the subretinal space (Hanke-Gogokhia et al., 2021). Aquaporin-1, a transmembrane channel that mediates water transport, is also apically expressed (Stamer et al., 2003; Juuti-Uusitalo et al., 2013). As the apical side is the site of photoreceptor outer segment phagocytosis, it is enriched with receptor αvβ5 (Finnemann et al., 1997), scavenger receptor CD36 (Ryeom et al., 1996), and Mer tyrosine kinase (Mertk) (Gal et al., 2000; Vollrath et al., 2001; Feng et al., 2002).

Some proteins are expressed ubiquitously in RPE cells. For example, Glut1 is evenly distributed across both the apical and basolateral surfaces, facilitating efficient glucose transport between choroid and photoreceptors through the RPE (Sugasawa et al., 1994). Ezrin is needed for the proper formation of microvilli and basal infoldings in RPE cells (Bonilha et al. 1999, 2006; Kivelä et al., 2000).

RPE polarity is also reflected in the distinct spatial arrangement of

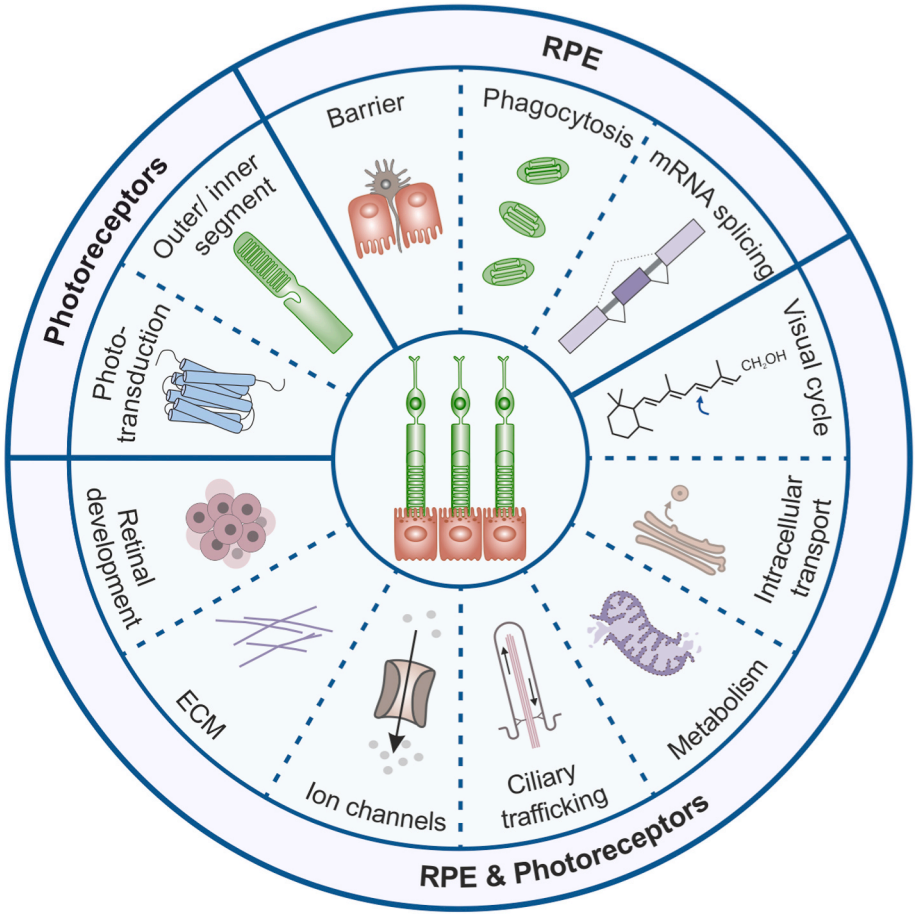

Fig. 1. Functional Classification of RP-associated Genes. RP-associated genes are categorized into twelve major biological processes. Genes involved in phototransduction and outer/inner segment morphogenesis are exclusively expressed in rod photoreceptors. In contrast, genes related to barrier function, phagocytosis, and mRNA splicing are expressed in the RPE, with mutations in these genes leading to RP through RPE dysfunction. Genes in the remaining categories—visual cycle, intracellular transport, metabolism, ciliary trafficking, ion channels, extracellular matrix (ECM), and retinal development—are expressed in photoreceptors and/or RPE. Mutations in any of these gene groups can impair the photoreceptor and/or RPE function, ultimately contributing to the progressive vision loss characteristic of RP.

organelles. The nucleus, Golgi apparatus, and mitochondria are basally located (Sparrow et al., 2010), while the smooth endoplasmic reticulum and lysosomes are distributed throughout the cell. The melanosomes are membrane-bound organelles that move to the apical processes in a light-dependent manner (Futter et al., 2004). A representative ultrastructural image illustrates the apical concentration of melanin granules and the basal positioning of the nucleus (Fig. 2).

The maintenance of asymmetric protein distribution is regulated by different protein complexes that control cell polarity and junction formation, such as scribble (Yamanaka and Ohno, 2008; Segurado et al., 2022), ezrin (Kivelä et al., 2000), and the ESCRT-I component Tsg101 (Le et al., 2021).

4. Structural and molecular alterations in RPE observed in RP

In the following section, we discuss the structural changes of RPE cells that stem from mutations in RPE genes and how these changes impact their functions. In the second part, we focus on how photoreceptor degeneration leads to substantial alterations of RPE cells. Evaluating these changes is crucial for developing therapeutic strategies that address the retina holistically, considering other cell types beyond the primary affected target cell. This highlights the importance of understanding the correlation between the timing and severity of RPE alterations and the progression of photoreceptor degeneration. However, we acknowledge the limitations associated with this issue. For example, postmortem tissues provide histological evidence of RPE alterations, but only a handful of studies have included the patient's gene mutations. Thus, it remains unclear whether these changes arise from mutations in RPE-specific genes or occur as a consequence of photoreceptor death. Moreover, the limited availability of postmortem tissue from RP patients at early disease stages makes it challenging to study the initial alterations in the RPE.

In addition to postmortem analyses, our knowledge of cellular and molecular changes in RPE cells comes from animal and in vitro models that endeavor to replicate the human pathophysiology of RP. The most commonly used in vitro models are RPE cell lines and stem cell-derived RPE cultures. For a comprehensive overview of these models and their applications, readers are referred to (Lakkaraju et al., 2020). The most widely used RPE cell line is ARPE-19, a spontaneously immortalized line derived from the retina of a 19-year-old male, first described by (Dunn et al., 1996). These cells display several features of native RPE, including a polarized monolayer, a cobblestone morphology, pigmentation, and the expression of RPE-specific transcripts such as *CRALBP* and *RPE65*. Despite these advantages—such as ease of use, scalability, and reproducibility—ARPE-19 cells exhibit several limitations (Pfeffer and Fliesler, 2022). These include low transepithelial electrical resistance (TEER) (Dunn et al., 1996; Ablonczy et al., 2011), chromosomal abnormalities (Fasler-Kan et al., 2018), and reduced expression of many native RPE marker genes. TEER is widely used as a quantitative measure of tight junction integrity and epithelial barrier function, both of which are

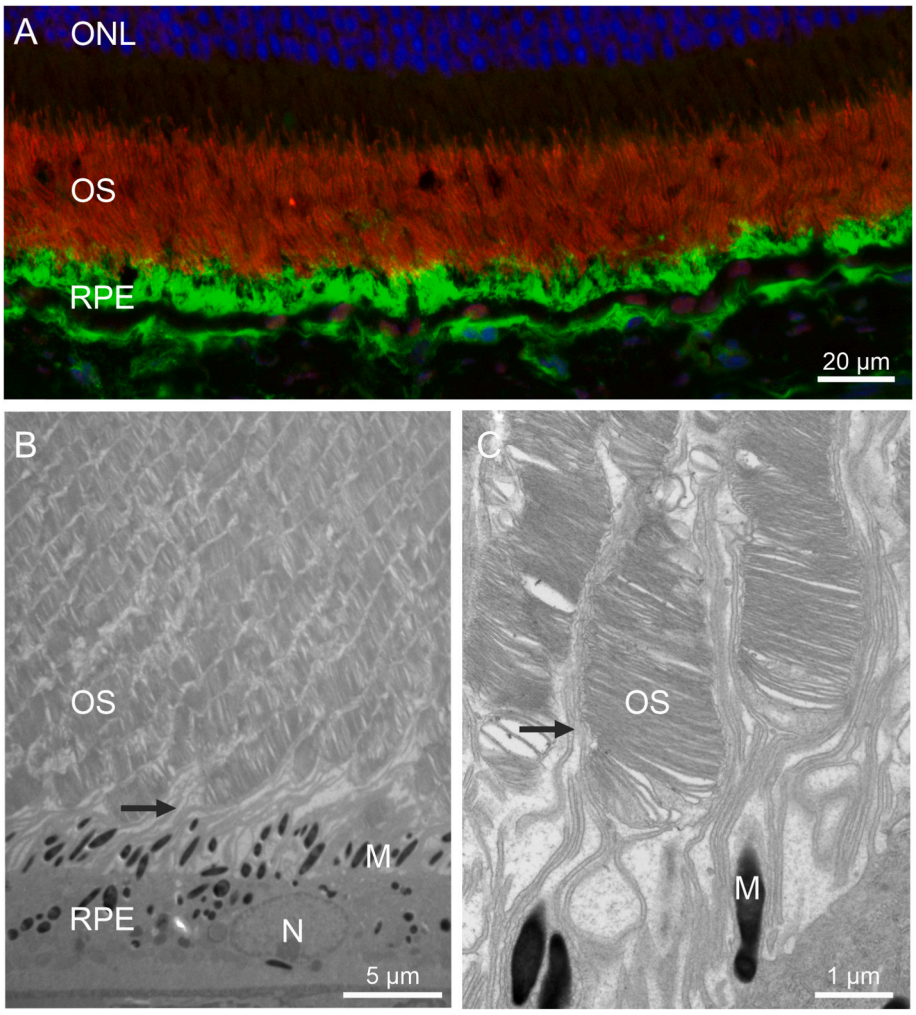

Fig. 2. RPE Microvilli Interdigitate with Photoreceptor Outer Segments. (A) Representative image of a retinal section from a 33-week-old wild-type mouse, immunostained for Ezrin (green), a marker of RPE apical microvilli, and PDE6B (red), labeling rod photoreceptor outer segments (OSs). The image highlights the close proximity between the RPE and rod photoreceptors. (B,C) Transmission Electron Microscopy (TEM) images from a 32-week-old wild-type mouse retina. (B) Polarized RPE cells exhibit apical microvilli (black arrow) that interdigitate with the photoreceptor OSs. Electron-dense melanin pigment granules (M) are concentrated in the apical processes, while the nucleus (N) is located basally. Adapted from (Koch et al., 2017). (C) High-magnification TEM image showing RPE microvilli engulfing rod photoreceptor OS tips (black arrow). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

essential for proper RPE physiology (Wang et al., 2022). Modifications to culture conditions and media composition have significantly improved ARPE-19 cell performance. These advances include enhanced differentiation, better morphology and polarity, increased expression of RPE-specific genes such as BEST1, MERTK, and ITGB5 (Ahmado et al., 2011; Hazim et al., 2019), and improved TEER measurements (Fragoso et al., 2012; Samuel et al., 2017), all of which are essential for RPE functionality.

RPE cells derived from induced pluripotent stem cells (iPSCs) closely mimic native RPE in morphology, gene expression, and function (Buchholz et al., 2009; Regha et al., 2022). These cultures can produce RPE cells that retain key characteristics of native RPE, including cellular architecture, RPE-specific protein expression, and robust TEER values (Hu and Bok, 2001; Sonoda et al., 2009; Hazim et al., 2017). The generation of stem cell-derived RPE cultures requires optimized differentiation protocols (Surendran et al., 2022). An important feature of iPSC-derived RPE is the ability to generate patient-specific cells, which enables modeling of disease-relevant mutations and supports mechanistic studies (Brydon et al., 2019; Vázquez-Domínguez et al., 2022). Despite these advances, in vitro models still fail to recapitulate the interconnection between RPE cells and photoreceptors. Taking this into account, the results must be interpreted with caution when attempting to correlate laboratory observations with descriptive clinical data.

Mutations in genes expressed in RPE (18 genes) account for around 15 % of RP causative genes, summarized in Table 2. Structural and morphological changes in RPE cells include altered polarity, loss of intercellular junctions and cell-to-cell contact, changes in cell size and shape, vacuolization, loss of apical microvilli and basal infoldings, and migration to the subretinal space (Figs. 3 and 4). The CRB1 protein, encoded by the Crumbs homolog 1 (*CRB1*) gene, is a member of the Crumbs complex and plays an essential role in maintaining cell polarity and retinal morphogenesis (Mehalow et al., 2003). Mutations in *CRB1* have been associated with retinal degenerations, including RP (den Hollander et al., 1999; Bujakowska et al., 2012). CRB1 is a transmembrane protein and is expressed in Müller glial cells (van Rossum et al., 2006), in the vicinity of the outer limiting membrane of photoreceptors' inner segments (van de Pavert et al., 2004), and at the apical junctional complex of RPE cells (Peng et al., 2024). Disruption of the outer limiting membrane and formation of retinal folds (pseudorosettes) have been observed in the naturally occurring *Crb1* mouse mutant rd8 (Peng et al., 2024)

Polarity defects have been reported in iPSC-derived RPE cells

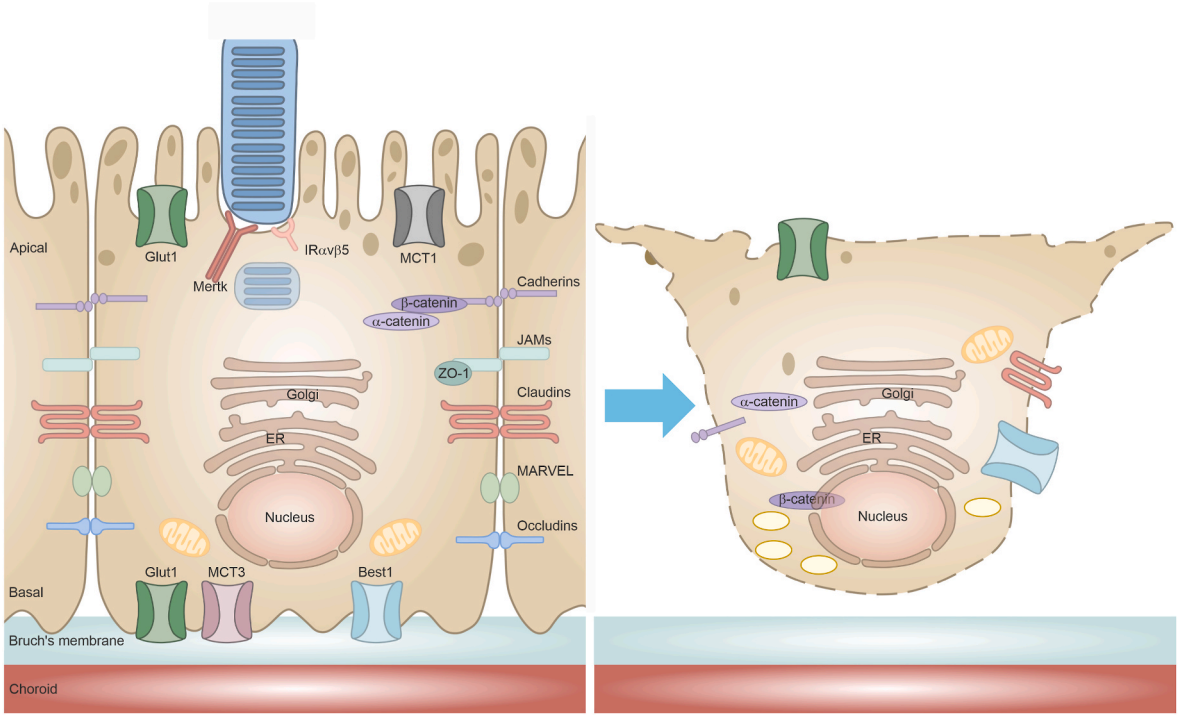

Fig. 3. Healthy and Pathological Phenotypes of RPE in RP. The RPE is a monolayer of polarized cells, with the apical surface interfacing with photoreceptor outer segments and the basal surface anchored to Bruch's membrane and the choroid. RPE cells exhibit distinct apical-basal polarity, reflected in their specialized distribution of organelles and membrane proteins. On the basal membrane, transporters such as Glucose Transporter 1 (GLUT1) and Monocarboxylate Transporter 3 (MCT3), and ion channels such as Bestrophin-1 (BEST1) are expressed, along with the localization of the nucleus, endoplasmic reticulum (ER), and mitochondria. The apical membrane expresses GLUT1, Monocarboxylate Transporter 1 (MCT1), and phagocytosis receptors such as MerTK and integrins, with melanosomes highly enriched on this side. Lateral membranes are interconnected via tight junctions (e.g., occludins, claudins), scaffolding proteins (e.g., ZO-1), and adherens junction components (e.g., cadherins, α-catenin, and β-catenin). In RP, RPE cells undergo both structural and molecular alterations. These include disruption of apical-basal polarity, disorganization of tight junctions, loss of intercellular contact, and impaired barrier function. α-catenin translocates to the cytoplasm, and β-catenin accumulates in the nucleus, contributing to cellular dysfunction.

Table 2
RPE-expressed genes associated with RP, their functions, subcellular localization, and the number of RP-linked mutations. Mutation data were retrieved from the Human Gene Mutation Database (HGMD®).

Gene (Protein)	Function	Subcellular Localization	RP-Associated Mutations (Total Known Mutations)	Other Associated Retinal Diseases	References
ADIPOR1	DHA uptake	Apical	2 (6)	Bardet-Biedl Syndrome	(Xu et al., 2016; Zhang et al., 2016)
ARHGEF18	Epithelial Barrier Integrity	Plasma Membrane	5 (7)		Arno et al. (2017)
BEST1	Ca^{2+}-activated Chloride Channel	Basal Plasma Membrane	5 (356)	Best Disease	Zhu et al. (2022)
CRB1	Epithelial Barrier Integrity	Apical	119 (388)	Leber Congenital Amaurosis	(den Hollander et al., 1999; Paun et al., 2012)
CRB2	Epithelial Barrier Integrity	Apical	1 (29)		Chen et al. (2019)
LRAT	Visual Cycle	Endoplasmic Reticulum	7 (26)	Leber Congenital Amaurosis	(Chen et al., 2018; Talib et al., 2019)
MERTK	Phagocytosis	Apical	39 (114)		Poli et al. (2023)
PRPF3	mRNA splicing	Nucleus	6 (9)		Zhong et al. (2016)
PRPF4	mRNA splicing	Nucleus	3 (5)		Chen et al. (2014)
PRPF6	mRNA splicing	Nucleus	4 (15)		Tanackovic et al. (2011)
PRPF8	mRNA splicing	Nucleus	35 (58)		Xu et al. (2018)
PRPF31	mRNA splicing	Nucleus	117 (213)		Kiser et al. (2019)
RDH5	Visual Cycle	Endoplasmic Reticulum	2 (56)	Congenital Stationary Night Blindness	Sultan et al. (2018)
RGR	Visual Cycle	Internal Membranes	7 (12)	Chorioretinal Atrophy	(Morimura et al., 1999; Li et al., 2016)
RLBP1 (CRALBP)	Visual Cycle	Cytosol/Plasma Membrane	9 (40)	Retinitis Punctata Albescens	Maw et al. (1997)
RPE65	Visual Cycle	Endoplasmic Reticulum	32 (243)	Leber Congenital Amaurosis	(Morimura et al., 1998; Bjeloš et al., 2022)
SEMA4A	Endosomal Sorting	Apical Plasma Membrane	2 (16)	Cone or Cone-Rod Dystrophy	Abid et al. (2006)
TBC1D32	Ciliogenesis	Primary Cilium	1		Bocquet et al. (2023)

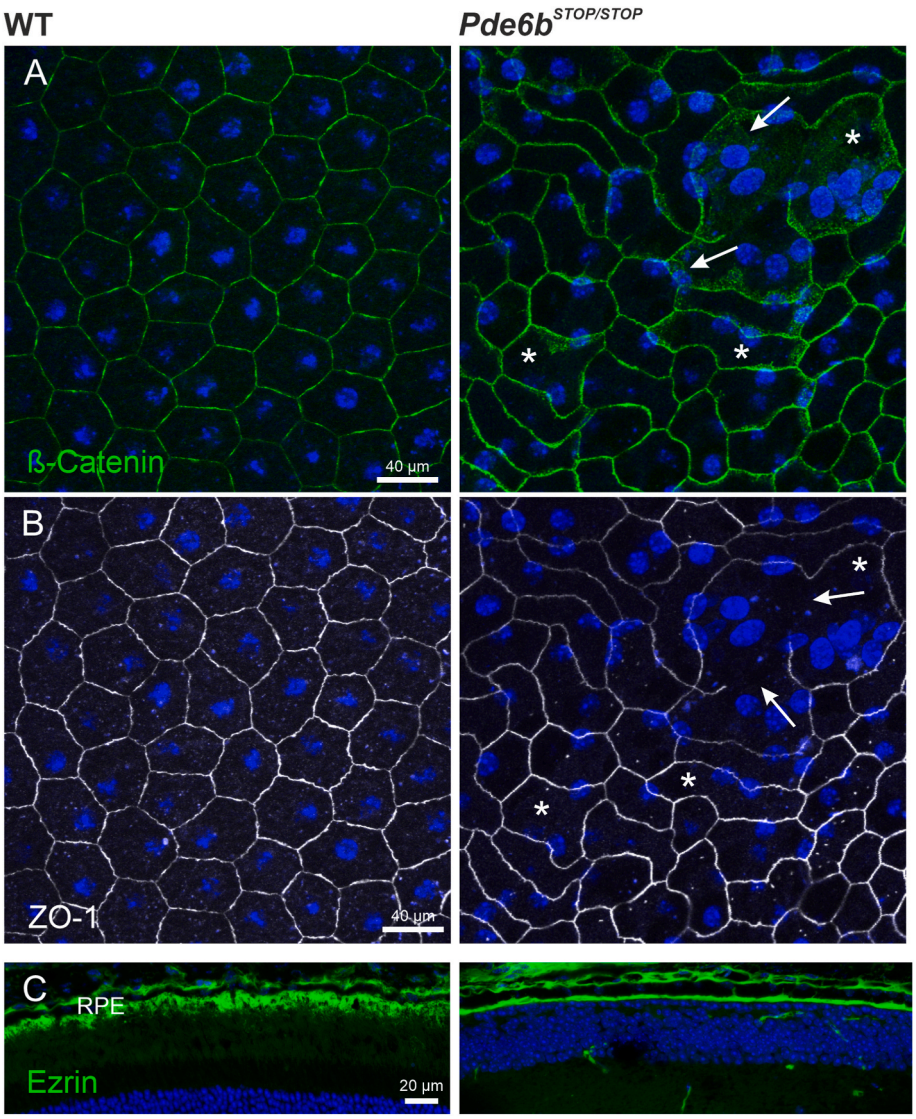

Fig. 4. Structural Changes in the RPE Observed in the RP Mouse Model *Pde6b*$^{STOP/STOP}$. (A, B) Representative images from RPE-choroid-sclera flatmounts from 33-week old WT and 34-week old *Pde6b*$^{STOP/STOP}$ mice, immunolabeled with anti-β-catenin (green) (A), a component of adherens junctions, and anti-ZO-1 (white) (B), a tight junction scaffold protein. Flatmounts from *Pde6b*$^{STOP/STOP}$ mice show regions with abnormal cell morphology and size (white stars), cytoplasmic redistribution of β-catenin (arrows), and disrupted ZO-1 junctional patterning (arrows). (C) Representative retinal sections from 33-week old WT and 32-week old *Pde6b*$^{STOP/STOP}$ mice, immunostained for Ezrin, a marker for the RPE apical microvilli, reveal abundant microvilli in WT mice, while *Pde6b*$^{STOP/STOP}$ mice exhibit a near-complete loss of Ezrin-positive microvilli. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

obtained from RP patients carrying mutations in *PRPF* genes encoding different pre-mRNA processing factors (PRPFs). Defects in splicing factors, including PRPF13 (Buskin et al., 2018), PRPF6 (Liang et al., 2022), and PRPF8 (Arzalluz-Luque et al., 2021), evoked missplicing of genes involved in cell adhesion, leading to disorganized apicobasal polarity. Additionally, new pathogenic variants in *TBC1D32* have been associated with RP, with patients' iPSC-derived RPE cells exhibiting disrupted apical tight junctions (Bocquet et al., 2023).

These structural changes seem to be the initiating event for an epithelial-mesenchymal transition (EMT), a cellular process where epithelial cells undergo multiple changes, leading to the downregulation of epithelial and acquisition of mesenchymal features. While epithelial cells are polarized, terminally differentiated, and reside on a basal membrane, mesenchymal cells are non-polarized cells with migratory capacity (Yang et al., 2020). Preclinical and clinical studies reported the occurrence of EMT in RPE cells in retinal diseases such as AMD and proliferative vitreoretinopathy (PVR) (Tamiya and Kaplan, 2016; Ghosh et al., 2018), while only recently has the topic been getting attention in RP. In *TBC1D32* pathogenic iPSC-derived RPE, islands of upregulated vimentin expression, an EMT marker, concomitant with the loss of MERTK expression, were noted, suggesting the loss of RPE identity. Like CRB1, CRB2 is also expressed in the RPE (Paniagua et al., 2015). A homozygous *CRB2* p.R1249G mutation has been identified as a novel RP-causing variant (Chen et al., 2019) and was shown to trigger EMT in vitro (Chen et al., 2019).

Interestingly, RP patients with mutations in genes expressed primarily in rods show RPE atrophy that progresses in response to photoreceptor loss. An important question arises: how do pathological changes in rods promote impairment in RPE homeostasis? In the following section, we provide a comprehensive overview of the structural and topological changes of RPE cells as a secondary repercussion of photoreceptor loss. These include: discontinuities in ZO-1 pattern, changes in cell shapes and sizes, appearance of vacuoles, and shifts in the expression of catenin. We then discuss how these changes lead to

RPE invasion into the neural retina.

Abnormalities in RPE cells were reported in different RP mouse models. For example, in *Tvrm4* mice carrying a light-inducible mutation in the rhodopsin gene, changes in RPE cell size and shape, and disruptions in the ZO-1 pattern were detected as early as one week after induction (Zhang et al., 2019; Napoli et al., 2021; Napoli and Strettoi, 2023). Similar alterations were observed in the slowly progressive rd9 mice, which carry a mutation in ORF-15 of the RPGR gene, responsible for nearly 60 % of disease-causing RPGR mutations (Vervoort et al., 2000). In 12-month-old mice, where 65 % of photoreceptors remain, a decrease in ZO-1 immunofluorescence (Falasconi et al., 2019) and distorted RPE cells were observed (Napoli et al., 2021). The rd10 mouse model, which carries a mutation in the *Pde6b* gene, exhibits interruptions in ZO-1 staining (Napoli et al., 2021) along with alterations in RPE cell shape and size (Jiang et al., 2013). The changes in the rd10 mice were classified into zones following a bullseye pattern. In the posterior zone, around the optic nerve, RPE cells become larger, irregular, and variable in shape. In the mid-periphery, the cells exhibit a compressed morphology, while in the periphery, they maintain their shape and size until the late stages (Chrenek et al., 2012). A similar pattern was observed in $Pde6b^{STOP/STOP}$ mice, which contain a STOP-cassette in the *Pde6b* gene. In the central RPE, cell size was irregular, with both abnormally large and small cells present. RPE cells in the equatorial region exhibited strikingly elongated shapes (Kajtna et al., 2022). Irregularities in RPE cell size and shape have also been documented in the $Pde6g^{-/-}$ (Jentzsch et al., 2023) and the rd1 mouse models (Wu et al., 2021), as well as in P23H-1 rats, which carry a proline to histidine mutation in the rhodopsin gene—the most common autosomal dominant mutation in North America (Valiente-Soriano et al., 2020). Discontinuities in ZO-1 profiles were concomitant with leakage and loss of the outer RBB (Falasconi et al., 2019; Napoli et al., 2021). A breakdown of BRB has also been observed in patients with RP (Vinores et al., 1995).

Additional ultrastructural abnormalities, identified through electron microscopy, revealed the presence of membranous vacuoles at the RPE leaflets adjacent to areas of complete photoreceptor degeneration. These vacuoles were concentrated at the basal side of the RPE in rd9 and *Tvrm4* mice (Napoli et al., 2021; Napoli and Strettoi, 2023), while cytoplasmic vacuolization was noted in the apical region of rd1 mice (Wu et al., 2021). The presence of these vacuoles suggests a defective ability of the RPE to regulate fluid buildup and maintain electrolytic balance. Such occurrences have also been observed during aging (Chen et al., 2016) and in mouse models with defects in autophagy (Valapala et al., 2014).

Increased α-catenin translocation from the membrane to the cytosol was detected in *Tvrm4* mice (Zhang et al., 2019). α-catenin is an actin-binding and actin-bundling protein that connects the cadherin-catenin complex to the actin cytoskeleton at adherens junctions (Rimm et al., 1995; Ishiyama et al., 2018). It is also associated with ZO-1 (Van Itallie et al., 2013), and disruption of this interaction compromises tight junction integrity and the epithelial barrier (Maiers et al., 2013). Diffuse cytoplasmic β-catenin was observed in $Pde6b^{STOP/STOP}$ mice (Kajtna et al., 2022). Normally, β-catenin localizes to the adherent junctions of the RPE (Kim et al., 2023), but it relocalizes to the cytoplasm and the nucleus upon oxidative stress exposure (Narimatsu et al., 2013) and during EMT (Kim et al., 2008).

The loss of RPE cell polarity and morphological hallmarks, i.e., the hexagonal shape and tight junctions, suggests that RPE cells exhibit signs of EMT, potentially serving as the initiation event for their migration into the neural retina. However, there is no evidence of EMT in RP patients (for instance, detection of specific markers of EMT in postmortem tissues). Early studies in RP patients reported that, following photoreceptor degeneration, RPE cells detach from Bruch's membrane and migrate deep into the neural retina, where they accumulate around (hypertrophic) blood vessels (Rodrigues et al., 1985; Li et al., 1995; Milam et al., 1998). Due to their branching pattern and the presence of black melanin granules, these RPE-pigmented deposits were termed "bone spicules". These spicules are hypothesized to function as a scaffold to facilitate the migration of other cells throughout the retina (Jones et al., 2016). Histopathological studies showed that the translocated RPE cells are remarkably polarized, with filopodia processes extending from their apical surfaces and connections maintained by tight junctions (Li et al., 1995) or desmosomes (Rodrigues et al., 1985). Whether the displaced cells will preserve their polarity after invasion or undergo dedifferentiation remains unclear. Migrated pigmented cells have been reported to reach the inner retina individually or as RPE sheets (Li et al., 1995); however, detailed descriptions of each case were not provided. Another study on a patient with advanced RP showed that RPE cells adjacent to surviving cones were larger than normal and exhibited apically displaced nuclei, indicative of a loss of polarization. Nevertheless, the authors noted minimal invasion of RPE into the retina (Szamier and Berson, 1977).

In line with the clinical data, migration of RPE cells into the neural retina has been reported in various animal models. In P23H rat models, this migration likely corresponds to invasion of blood vessels accompanied by RPE (Pinilla et al., 2016). In rd10 mice, RPE cells exhibit a compressed or convoluted morphology, appearing to be detached from Bruch's membrane and forming multiple layers beneath the retina (Chrenek et al., 2012). Studies in $Rho^{-/-}$ mouse models suggest that the proximity of retinal vessels to the RPE triggers the migration of RPE cells along the contacting vessels toward the inner retina. Ultrastructural analysis revealed that these mislocalized RPE cells partially sealed the vessels through tight junctions and deposited extracellular matrix in a perivascular location (Jaissle et al., 2010).

The stimulus responsible for the structural alterations of RPE cells, particularly when the primary affected cell type is rod photoreceptors, remains unclear, and many processes have been proposed. One hypothesis suggests that inflammation in the retina following photoreceptor death may trigger the impairment of RPE tight junctions and BRB breakdown. An increased number of immune cells, such as microglia and macrophages, have been found in areas with abnormal ZO-1 distribution (Napoli et al., 2021; Napoli and Strettoi, 2023). The authors proposed that activated immune cells release metalloproteases and cytokines that could regulate ZO-1 expression, leading to barrier dysfunction, a phenomenon also observed in early diabetic retinopathy (Giebel et al., 2005). Interestingly, alterations in ZO-1 levels have been shown to impact RPE cell proliferation, morphology, and differentiation, including increased expression of EMT markers (Georgiadis et al., 2010).

5. How do the RPE alterations contribute to RP pathogenesis?

Retinal function depends on an interplay between the photoreceptors and RPE cells. Photoreceptors maintain an intimate physical interaction with the RPE, with the tips of their outer segments interdigitating with the apical microvilli of the RPE. Several lines of evidence pointed out the involvement of the RPE in the biogenesis of photoreceptor outer segments. Bumsted et al. (2001) used Microphthalmia-associated transcription factor (MITF) mutant mice, which fail to undergo RPE differentiation, and showed that outer segments do not elongate in the absence of apical microvilli. Similarly, ablation of RPE cells via diphtheria toxin expression resulted in defective retinal morphogenesis (Raymond and Jackson, 1995). Knockdown of DNA methyltransferase 1 (*Dnmt1*) in RPE compromised its apicobasal polarity, disrupted photoreceptor development, and impaired outer segment morphogenesis (Nasonkin et al., 2013). One of the significant limitations of retinal organoids is their inability to develop functionally mature outer segments (Zhong et al., 2014), probably due to the absence of RPE-derived support. It has been suggested that RPE apical microvilli provide structural or metabolic support to promote disc stacking during outer segment elongation (Bumsted et al., 2001). Notably, the supplementation with antioxidants and lipids promoted the formation of organized outer segments in retinal organoids (West et al., 2022). Additionally,

adiponectin receptor 1 (AdipoR1), expressed in both photoreceptor and RPE cells, regulates docosahexaenoic acid (DHA) uptake and incorporation into photoreceptor outer segment membranes (Rice et al., 2015). ADIPOR1 deficiency reduces DHA uptake from the circulation (Rice et al., 2015) and its subsequent transfer to photoreceptors, ultimately leading to photoreceptor degeneration (Kautzmann et al., 2020).

A central question concerns the impact of RPE cell loss on photoreceptor survival and integrity. Chowers et al. (2017) showed that intraperitoneal injection of sodium iodate induces rapid RPE cell loss, followed by photoreceptor degeneration a few days later, highlighting the crucial role of the RPE in photoreceptor survival. Similarly, a mouse model with conditional genetic ablation of RPE cells exhibited reduced photoreceptor function and the formation of retinal folds (Longbottom et al., 2009).

5.1. RPE-associated genes implicated in RP

Over the past decades, our understanding of the genetic architecture of RP has increased tremendously, due to advances in genome-wide and DNA sequencing technologies, with more than 119 causative genes identified. Among those, only 18 RP-causing genes are expressed and/or related to a function in RPE cells (Table 1). Some genes were shown to be expressed in both RPE and photoreceptors, including RPE65 (Boulanger and Redmond, 2002; Kolesnikov et al., 2018), AdipoR1 (Rice et al., 2015), and TBC1D32 (Bocquet et al., 2023). The following section reviews how genes expressed in the RPE map onto key pathophysiological mechanisms leading to RP, illustrated in Fig. 5.

5.1.1. Disruption of the visual cycle

The visual cycle, also known as the retinoid cycle, involves a series of biochemical reactions occurring in photoreceptors and RPE cells. The first step is initiated in the photoreceptor's outer segments by activating rhodopsin after light absorption. Rhodopsin, a G-protein-coupled receptor, consists of opsin and the chromophore 11-cis-retinal. Upon light exposure, 11-cis-retinal undergoes photoisomerization into all-trans-retinal, which is then released from opsin. All-trans-retinal is subsequently reduced to all-trans retinol in the photoreceptor outer segments and transported to the adjacent RPE via the retinol-binding protein 3 (RBP3). Within RPE cells, all-trans retinol is reisomerized into 11-cis retinal through a series of enzymatic steps. First, lecithin retinol acyltransferase (LRAT) converts all-trans retinol to all-trans retinyl-esters, which are then converted into 11-cis retinol by the retinoid isomerohydrolase RPE65. Next, different isoforms of retinol dehydrogenase (RDH) catalyze the oxidation of 11-cis retinol into 11-cis retinal. Cellular retinaldehyde–binding protein (CRALBP), a retinoid-binding protein, plays a crucial role in multiple steps of the visual cycle by increasing the isomerase activity of RPE65 and facilitating the oxidation of 11-cis-retinol to 11-cis-retinal (Saari and Crabb, 2005). Under photic conditions, the supply of 11-cis-retinal is insufficient to meet the demand. In the RPE, the retinal G-protein-coupled receptor (RGR) can compensate for the shortage by catalyzing the photoisomerization of all-trans-retinal to 11-cis-retinal (Tworak et al., 2023). Finally, the newly synthesized 11-cis retinal is transported back to the photoreceptors, where it regenerates the photosensitive visual pigment, completing the cycle.

Mutations in RPE-specific genes involved in the visual cycle have been linked to compromised photoreceptor function and are associated with different forms of RP. These include mutations in LRAT (Chen et al., 2018; Talib et al., 2019), RPE65 (Gu et al., 1997; Marlhens et al., 1997; Morimura et al., 1998; Bjeloš et al., 2022), RDH11 (Xie et al., 2014; Liu et al., 2022), human RLBP1 gene that encodes CRALBP (Maw et al., 1997), and RGR (Morimura et al., 1999; Li et al., 2016). Additionally, mutations in the upstream player Semaphorin 4A (Sema4A) have been reported to be associated with RP (Abid et al., 2006). Sema4A is involved in the sorting of the retinoid-binding proteins CRALBP and CRBP1 (cellular retinol-binding protein 1), predominantly under dark conditions, to regulate the uptake, regeneration, and transport of retinoids essential for phototransduction (Toyofuku et al., 2012). Pathogenic mutations result in the mislocalization of the Sema4A protein from the cell membrane to the endoplasmic reticulum in RPE cells, leading to impaired endosomal sorting of the retinoid-binding proteins.

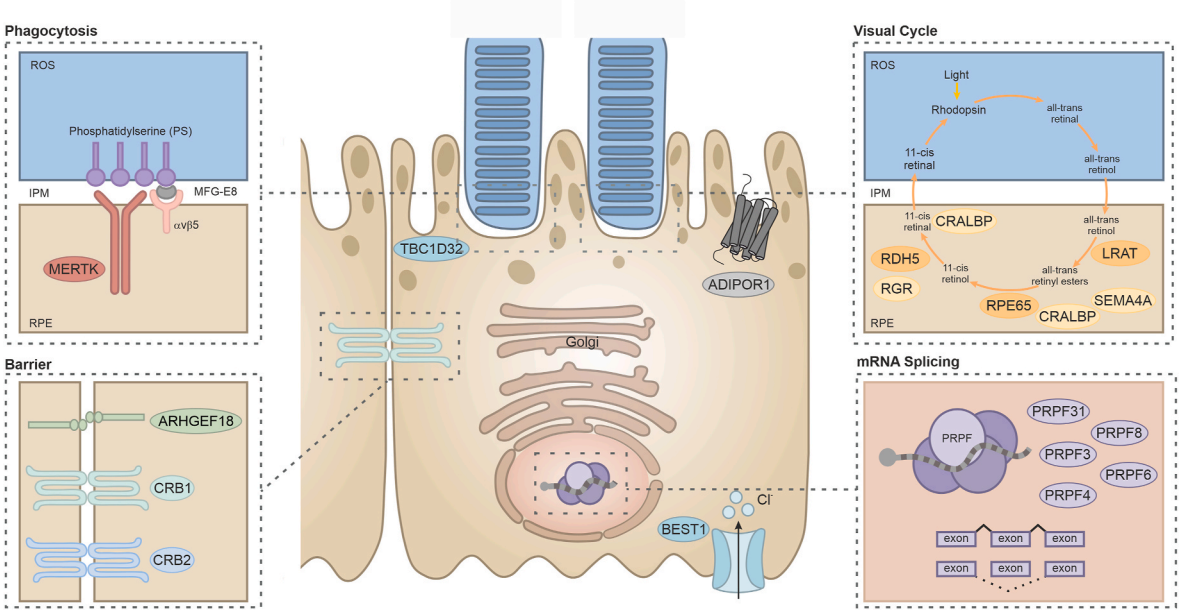

Fig. 5. RPE-Localized Proteins Implicated in RP Pathogenesis. Cellular localization of RP-associated proteins that are expressed in RPE. These include components of the visual cycle (lecithin retinol acyltransferase, LRAT; RPE-specific 65 kDa protein, RPE65; retinol dehydrogenase 5, RDH5; retinal G protein-coupled receptor, RGR; retinaldehyde-binding protein 1, RLBP1, also known as CRALBP; and semaphorin 4A, SEMA4A), cell-cell junctional and polarity regulators (TBC1 domain family member 32, TBC1D32; Crumbs homologs, CRB1 and CRB2, and Rho/Rac guanine nucleotide exchange factor 18, ARHGEF18), anion channel (bestrophin-1, BEST1), phagocytosis receptor (MER tyrosine kinase, MERTK), adiponectin receptor 1, ADIPOR1 and mRNA splicing factors (pre-mRNA processing factors, PRPF3, PRPF4, PRPF6, PRPF8, and PRPF31).

5.1.2. RPE barrier and transport dysfunction

The RPE barrier is formed by the tight junction complexes between the RPE cells and is essential for establishing an optimal microenvironment (Cunha-Vaz et al., 2011). It plays a critical role in preventing the entry of harmful substances and maintaining the retina's immune privilege. The contribution of RPE tight junctions in barrier defense was recently demonstrated by a study showing that a breach in epithelial barrier function led to photoreceptor degeneration in the Crb1 mutant (rd8) mice. CRB1 is expressed in RPE cells and colonic enterocytes (Peng et al., 2024). In this study, the authors showed that Crb1 mutant (rd8) mice have disrupted structures of adherent junctions at both the RPE and the colonic enterocytes. Thus, its loss led to impairment in the outer BRB and the intestinal epithelial barrier in the colon, leading to the translocation of gut bacteria to the retina and secondary photoreceptor degeneration. Notably, antibiotic treatment prevented this degeneration (Peng et al., 2024). These findings highlight how alterations in junctional integrity can trigger RPE barrier breach and lead to retinal degeneration.

Another Crumbs family member, *Crb2*, is also implicated in RP (Chen et al., 2019). Crb2 localizes to the RPE plasma membrane, and in vitro studies using ARPE-19 cells carrying *Crb2* mutations showed reduced RPE marker expression, disrupted tight junctions (marked by ZO-1), EMT, and impaired phagocytosis (Paniagua et al., 2015). Similarly, mutations in *TBC1D32*, associated with RP, led to EMT-like changes and defective apical tight junctions in iPSC-derived RPE cells (Bocquet et al., 2023), although in vivo implications remain to be explored.

Additionally, mutations in the gene encoding ARHGEF18 (also known as p114RhoGEF) have been associated with RP (Arno et al., 2017). ARHGEF18 is a junction-associated protein that regulates RhoA signaling, a key component of the junctional complex crucial for the maintenance of RPE polarity, tight junction localization, and cell proliferation (Terry et al., 2011; Herder et al., 2013). However, the exact role of ArhGEF18 mutations in RP is not elucidated yet, and it would be interesting to explore how such mutations might interfere with the maintenance of epithelial barrier integrity in the retina.

Another example of how impaired transepithelial transport can lead to RP comes from Bestrophin-1. Bestrophin-1 is an anion channel localized to the basolateral plasma membrane of RPE cells (Marmorstein et al., 2000; Bakall et al., 2003). While most *BEST1* mutations are associated with vitelliform macular dystrophy (Marquardt et al., 1998; Petrukhin et al., 1998), some are linked to RP (Davidson et al., 2009; Dalvin et al., 2016). Bestrophin-1 has been shown to act as a calcium-activated Cl^--channel (Moshfegh et al., 2016), and also plays a role in regulating voltage-gated Ca^{2+} channels in an RPE cell line (Rosenthal et al., 2006). The RP-associated mutations lead to mislocalization of Bestrophin-1 from the basolateral membrane to the cytoplasm and reduce chloride conductance (Davidson et al., 2009).

5.1.3. Impaired phagocytosis of photoreceptor outer segments

The termination of phototransduction requires the bleaching of rhodopsin, which eventually leads to phototoxic damage to the proteins and lipids within the rod outer segment discs (Organisciak and Vaughan, 2010). Since photoreceptors are non-dividing cells, they depend critically on the turnover of their discs to prevent the accumulation of damaged macromolecules. Seminal studies in the early 1960s demonstrated that RPE cells phagocytose photoreceptor outer segments (Dowling and Gibbons, 1962; Dowling and Sidman, 1962; Young and Bok, 1969). This process involves the daily phagocytosis of shed discs by the RPE, synchronized with the synthesis and assembly of new discs at the base of the outer segment. One complete cycle (ie, all disks replaced) requires approximately two weeks. Through this mechanism, RPE cells ensure the maintenance of long-lived photoreceptors (Kwon and Freeman, 2020). Photoreceptor outer segment shedding and their subsequent phagocytosis is a highly disciplined process that follows a strict diurnal rhythm, taking place at light onset (Besharse et al., 1977; Goldman et al., 1980).

The phagocytic process can be divided into three major phases: 1) recognition and binding, 2) engulfment, and 3) digestion and elimination. The primary "eat me" signal for RPE cells is the externalization of phosphatidylserine (PS) on the outer leaflet of outer segments, which peaks shortly after light onset (Ruggiero et al., 2012). RPE cells require the phagocytosis receptor αvβ5 integrin–dependent signaling to synchronize circadian photoreceptor shedding with their phagocytic activity (Nandrot et al., 2004). The integrin ligand milk fat globule-EGF Factor 8 (MFG-E8), located in the subretinal space, acts as a soluble bridge between externalized PS on outer segments and the integrin receptors αvβ5 on RPE cells (Burgess et al., 2006; Nandrot et al., 2007). The binding of outer segments to integrin receptor αvβ5 stimulates the mobilization and activation of focal adhesion kinase (FAK), ultimately leading to the phosphorylation and activation of Mer Tyrosine Kinase (MerTK) (Finnemann and Nandrot, 2006; Prasad et al., 2006). MerTK promotes the engulfment and internalization of outer segments by stimulating branched actin polymerization and recruiting a number of adaptors and effectors. Finally, the phagocytosis process involves the coordinated activities of numerous proteins, determining whether individual outer segment components undergo degradation or are recycled back to photoreceptors for reuse (Mazzoni et al., 2014).

Given the critical role of phagocytosis in maintaining retinal homeostasis, it is reasonable to assume that failure of RPE cells to phagocytose outer segment tips could lead to debris accumulation in the subretinal space, ultimately compromising photoreceptor function. However, although knockout mouse models of integrin receptor αvβ5 exhibited a loss of synchronized photoreceptor outer segment phagocytosis as early as the onset of retinal maturation, along with the accumulation of autofluorescent lipofuscin by one month of age, a decline in photoreceptor function was only observed at later stages, around six months (Nandrot et al., 2004). Intriguingly, the loss of MFG-E8, the ligand for αvβ5 integrin receptors, does not replicate the effects of αvβ5 receptor loss on retinal function. Mice lacking MFG-E8 do not show a decrease in visual function over time (Nandrot and Finnemann, 2008), suggesting that alternative compensatory mechanisms may mitigate its absence.

Using a positional cloning approach followed by in vivo genetic complementation experiments (D'Cruz et al., 2000; Vollrath et al., 2001), identified *Mertk* as the responsible gene for the retinal dystrophy phenotype observed in the Royal College of Surgeons (RCS) rat model (Chinchore et al., 2017; Dowling and Sidman, 1962a; Strauss et al., 1998). RPE cells from RCS rats exhibit a defect in outer segment phagocytosis (Edwards and Szamier, 1977; Chaitin and Hall, 1983), demonstrating that MERTK is essential for RPE phagocytosis (Feng et al., 2002; Burstyn-Cohen et al., 2012). Consistent with the RCS rat phenotype, $Mertk^{-/-}$ mice show early retinal degeneration (Duncan et al., 2003; Burstyn-Cohen et al., 2012). Interestingly, the severity of photoreceptor degeneration in $Mertk^{-/-}$ mice varies depending on genetic background (Vollrath et al., 2015). In humans, mutations in *MERTK* have been associated with different retinal dystrophies (Mackay et al., 2010; Audo et al., 2018), including RP (Gal et al., 2000; Ostergaard et al., 2011). However, not all patients with *MERTK* mutations exhibit the same clinical manifestations or disease severity (Tschernutter et al., 2006), suggesting that genetic factors or environmental modifiers influence *MERTK*-associated retinal degeneration phenotypes (Vollrath et al., 2015; Akalu et al., 2022). Two recent studies further support this idea by suggesting novel roles for *MERTK* beyond its well-established role in phagocytosis.

(Mercau et al., 2023) investigated the role *Mertk* using mouse models with concomitant hypomorphic expression or loss of function of *Tyro3* in a *Mertk*-null background. *TYRO3* is a paralogue of *MERTK* from the TAM family of receptor tyrosine kinases and has been identified as a genetic modifier in $Mertk^{-/-}$ mice (Vollrath et al., 2015; Akalu et al., 2022). These mice exhibited a broad-spectrum RPE inflammatory response, detectable even before eye-opening and prior to any histological signs of retinal degeneration. Notably, the early onset of RPE inflammation

suggests that it is not a consequence of failed phagocytosis but rather a causative component in retinal degeneration. Another study by (Iker Etchegaray et al., 2023) showed that Mertk-mediated phagocytosis in the retina contributes to promoting local insulin production, which will be discussed in later sections of this review.

Taken together, recent findings challenge the idea that MERTK-associated RPE dystrophy and retinal degeneration phenotype are solely due to its role in phagocytosis. Different *MERTK* mutations can result in distinct functional alterations, leading to variable phenotypic outcomes.

5.1.4. Impaired RNA splicing activities

Mutations in genes coding for pre-mRNA processing factors, such as PRPFs, SNRNP200, and PAP-1, have been linked to different types of RP (McKie et al., 2001; Xia et al., 2004; Tanackovic et al., 2011b; Yang et al., 2021). PRPFs are essential components of the U4/U6/U5 tri-snRNP complex, which is critical for the assembly of the mature spliceosome responsible for removing noncoding introns and joining exons in precursor messenger RNAs (pre-mRNAs) (Scotti and Swanson, 2016). Intriguingly, while these splicing factors are expressed ubiquitously and involved in fundamental cellular processes, mutations in these genes lead only to retinal diseases, including RP (Yang et al., 2021). Additional evidence points out that the RPE is the primary target of these mutations, with photoreceptor degeneration occurring secondary to RPE alterations (Graziotto et al., 2011).

A mouse model with common disease-causing missense mutations in *Prpf8* and *Prpf3* showed no significant photoreceptor degeneration or functional loss at 2 years of age. However, ultrastructural analyses revealed degenerative changes in RPE cells, such as the loss of basal infoldings, accumulation of amorphous deposits between the RPE and Bruch's membrane, and presence of vacuoles within the cells (Graziotto et al., 2011). Many RP patients with mutations in RNA splicing factors show relatively late disease onset, consistent with the late-onset phenotype observed in these mice (Zhao et al., 2006). Large-scale transcriptome analyses of retinal organoids derived from iPSCs of RP patients with mutations in the mRNA splicing factor *PRPF31* revealed mis-splicing of genes involved in ciliogenesis and cellular adhesion (Buskin et al., 2018). Severe RPE defects, including disrupted apical-basal polarity, reduced trans-epithelial resistance and phagocytic capacity, and shortened cilia length, were observed. Additionally, iPSC-derived RPE cells carrying a *PRPF6* mutation showed irregular morphology, aberrant apical microvilli organization, and reduced expression of RPE-specific genes such as *RPE65, MITF,* and *CRALBP*. These cells also displayed impaired phagocytosis, cell polarity, and barrier function (Liang et al., 2022). These findings suggest that the RPE may be the primary cell type affected by RP-associated *PRPF* mutations, leading to secondary photoreceptor degeneration. The selective vulnerability of RPE cells to mutations in these splicing factors remains unclear. The retina expresses higher levels of small nuclear RNAs (snRNAs) (Tanackovic et al., 2011b) and many RP-associated splicing factors, including *PRPF3, PRPF31* (Cao et al., 2011), compared to other tissues, which could reflect an elevated splicing activity. This suggests that mutations in splicing components may have particularly deleterious effects on the retina. Specifically, mutations in *PRPF6* show an RPE-specific phenotype, probably due to the misplicing and reduced expression of genes such as *RPE65, MITF,* and *CRALB*. Alternatively, the accumulation of unproductive mis-spliced RNAs may be more detrimental for the highly metabolic and phagocytotic RPE cells.

5.2. Molecular mechanisms by which the RPE alterations contribute to disease progression

Over the past few decades, significant progress has been made in understanding the pathobiology of RP, particularly regarding the structural and functional consequences for RPE cells following photoreceptor degeneration. Given the essential functions of the RPE, the question remains whether the RPE also contributes to cone photoreceptor cell death.

5.2.1. Loss of metabolic ecosystem between photoreceptors and RPE

Photoreceptors have high metabolic demands to sustain their neuronal activity and match their extensive need for metabolites. They shed around 10 % of their outer segments daily, requiring a continuous supply of metabolites to synthesize nucleotides, lipids, and proteins to drive the constant renewal of their outer segments. In the 1920s, Warburg observed that, similar to tumor cells, the retina consumes high levels of oxygen and performs aerobic glycolysis (Warburg, 1956). Aerobic glycolysis—that is glycolysis in an oxygen-rich environment—has been linked to the rapid cell proliferation and migration seen in tumor tissues, where cells reprogram their metabolism to enhance glycolysis and produce biosynthetic precursors that promote cell division, invasion, and migration (Zhou et al., 2022). Photoreceptors express high levels of glycolytic enzymes, including hexokinase 2 (HK2), pyruvate kinase M2 (PKM2), and lactate dehydrogenase (LDHA) (Chinchore et al., 2017; Petit et al., 2018; Rajala et al., 2016; Lee et al., 2023; Caruso et al., 2025). Studies in cats and rabbits have estimated that 50–90 % of the glucose delivered to the outer retina is converted to lactate via aerobic glycolysis (Ames and Li, 1992). Additionally, mutations in genes encoding key players in glucose metabolism have been linked to various inherited retinal diseases, including RP (Govers and Grimm, 2025).

The energetic dynamics of the photoreceptors cannot be understood if the photoreceptors are considered isolated cells (Chinchore et al., 2017; Hurley, 2021; Kanow et al., 2017). proposed a model of a symbiotic ecosystem between the RPE and photoreceptors. In this model, the high-energy-consuming photoreceptors depend on glucose, which reaches the outer retina from the choroidal vasculature via the RPE. GLUT1 is highly expressed on both the apical and basolateral membranes of the RPE, enabling efficient glucose diffusion (Gospe et al., 2010; Swarup et al., 2019). While insulin-dependent GLUT4 is typically absent in the retina under physiological conditions, its expression has been observed to be upregulated in mice upon starvation (Kanow et al., 2017; Iker Etchegaray et al., 2023). The RPE shuttles glucose to the retina, where photoreceptors metabolize it via aerobic glycolysis and produce lactate. The lactate is then shuttled back to the subretinal space through lactate transporters, where the RPE takes it up, converts it into pyruvate, and further metabolizes it via oxidative phosphorylation (OXPHOS). Together, the photoreceptors and RPE act as a symbiotic unit, ensuring that the energetic needs of both cell types are met.

One strategy to maintain such a symbiotic relationship between photoreceptors and RPE could be based on their differential preference for utilizing glucose as a source of energy. It was proposed that lactate derived from photoreceptors suppresses glycolysis in the RPE, thereby sparing glucose for the outer retina (Adijanto et al., 2014; Hurley et al., 2015; Kanow et al., 2017; Swarup et al., 2019). Cultured human fetal RPE cells (hfRPE) utilize lactate in vitro, and lactate in RPE cells can deplete NAD^+ by reducing it to NADH, suggesting that glycolysis may be disturbed when lactate is available (Kanow et al., 2017). Moreover, chronic hypoxia in RPE induced a shift into glycolysis and increased glucose intake, resulting in photoreceptor degeneration (Kurihara et al., 2016). Additionally, RPE utilizes other substrates to support its metabolic needs, thereby sparing glucose for the retina. The RPE can metabolize fatty acids from phagocytized outer segments to produce β-hydroxybutyrate, which can be used as a metabolic substrate for photoreceptors (Adijanto et al., 2014). Another study proposed that RPE cells have an exceptionally high capacity for reductive carboxylation of αKG to isocitrate, which might be a way for RPE cells to generate NADPH without consuming glucose (Du et al., 2016). RPE can also heavily use proline to fuel both its mitochondrial oxidative phosphorylation and reductive carboxylation pathways (Chao et al., 2017), but also to fuel retinal metabolism by exporting TCA cycle intermediates to the retina (Yam et al., 2019). Additionally, it has been shown that the retina releases and exports succinate to the RPE to fuel mitochondrial

respiration. In turn, the succinate is oxidized to malate, and exported to the retina to refuel succinate production via reverse SDH activity (Bisbach et al., 2020; Hass et al., 2022).

The effect of the RPE on aerobic glycolysis could also be related to its role in fibroblast growth factor 2 (FGF2) secretion, where RPE cells secrete FGF2, and inhibition of FGF signaling in vitro resulted in decreased lactate production, lower steady-state NADPH levels, and reduction in nascent RNA synthesis. This process can be reversed by culturing retina in the presence of the RPE complex, which increased the ability to produce lactate (Chinchore et al., 2017).

Understanding the energetic needs of the retina can only be relevant in the context of metabolic relationships between the photoreceptors and the RPE, or in other words, the retina ecosystem. The current dogma is that when RPE becomes more glycolytic, photoreceptors may degenerate due to a shortage of glucose. Indeed, blocking glycolysis in rods led to loss of outer segments, diminished function, and degeneration (Wang et al., 2011), while boosting glucose availability to photoreceptors and enhancing glycolysis slowed disease progression (Aït-Ali et al., 2015; Xu et al., 2018; Zhang et al., 2016).

(Swarup et al., 2019) used a mouse model that allows a 50 % reduction of GLUT1 expression in the RPE, which did not affect photoreceptor survival or function. However, when 70 % of GLUT1 expression was reduced, a shortening of the photoreceptor outer segments and cell death were observed, indicating that glucose transport via the GLUT1 transporter in the RPE is required to meet the anabolic and catabolic requirements of photoreceptors.

At the onset of rod outer segment shortening in RP, apical Glut1 expression was lost, leading to the accumulation of glucose in the RPE. During RP progression, the RPE activates glucose metabolism, including glycolysis, PPP, and glycogen synthesis, leading to diminished glucose transport to the photoreceptors. Glucose starvation in turn leads to photoreceptor starvation and vision loss in RP mouse model with dominant-acting P23H-*Rho* mutation (Wang et al., 2019). However, a study by (Brown et al., 2019) showed contradictory results, where a compensatory increase in RPE glycolytic metabolism resulted in only subtle alterations in mitochondrial functions without any reduction in function 5 months later. Due to the fact that most of these results were obtained from animal studies, it is difficult to make a clear conclusion about the effect of RPE dysregulated metabolism on photoreceptors.

Interestingly, P23H-*Rho* animal models show disrupted rods photoreceptor disks due to aggregation of misfolded mutant proteins (Sakami et al., 2011). This aggregation is thought to affect photoreceptors either directly—by inhibiting the synthesis of functional outer segments—or indirectly by increasing metabolic stress, which compromises the ability of the rods to sustain the high level of synthesis required to maintain outer segments. This ultimately leads to gradual outer segment shortening as RP progresses, eventually resulting in compromised glucose transport and dysregulated glucose metabolism in the RPE. Interestingly, MERTK has been shown to be required for apical Glut1 expression and for glucose transport from the RPE to photoreceptors. Its role in glucose metabolism was further supported by analysis of RNAseq data of *Mertk*-depleted RPE, which revealed reduced expression of *Ins2*, the gene encoding insulin (Penberthy et al., 2017; Akalu et al., 2022; Iker Etchegaray et al., 2023). These findings were experimentally validated, suggesting that the RPE acts as a local source of insulin. However, in contrast to systematic insulin signaling, insulin production was triggered by starvation, which also increased phagocytosis. Genetic deletion of *Mertk* reduced *Ins2* expression, whereas a *Mertk* gain-of-function construct increased *Ins2* production. Additionally, loss of *Ins2* decreased retinal glucose uptake and lactate production, along with reduced b-wave amplitude. It has long been hypothesized that insulin crosses the BRB to reach the neural retina via insulin receptors expressed throughout the retinal endothelial network (Reiter and Gardner, 2003). Punzo et al. (2009) reported changes in the insulin/mTOR pathway at the onset of cone degeneration, and demonstrated that systemic administration of insulin prolonged cone survival, whereas depletion of endogenous insulin had the opposite outcome. This protetective role of insulin may be due to its direct ability to suppress HIF-1α upregulation in cones, which normally occurs during degeneration. When rd1 mice were crossed with *Ins2* KO mice, a substantial reduction of cone cell numbers was observed (Iker Etchegaray et al., 2023). The RPE-derived insulin seems to be the main source for supporting cone viability, as no compensatory effect from the *Ins1* gene was observed.

Mutations in the *Abca4* gene have been associated with recessive Stargardt macular degeneration (STGD1), a subset of cone–rod dystrophies, and RP (Mullins et al., 2012). The ABCA4 protein is a flippase localized to the disk margins of photoreceptor outer segments, where it mainly functions to recycle retinaldehyde—a toxic photoproduct generated during the visual cycle. Mutations in ABCA4 that reduce or abolish this flippase activity result in the formation of toxic bisretinoids, which can directly damage the photoreceptors or accumulate in the underlying RPE, causing its dysfunction or loss, and subsequnelty leading to secondary photoreceptor degeneration. ABCA4 is also present in the RPE of mice, albeit at approximately 1 % of its abundance in the neural retina (Lenis et al., 2018). Genetically modified mice that express ABCA4 in the RPE but not in photoreceptor cells showed partial rescue of both lipofuscin accumulation and photoreceptor degeneration observed in *Abca4*$^{-/-}$ mice and in STGD1 patients, suggesting that the phenotypes in *ABCA4*-associated Stargardt disease are contributed by both RPE and photoreceptor pathologies. However, whether this is also the case for RP remains to be determined.

5.2.2. *Impaired antioxidant defense*

The retina is a highly oxygen-consuming organ that is continuously exposed to light, leading to the generation of significant amounts of reactive oxygen species (ROS). Additionally, the presence of photosensitizers and the high concentration of polyunsaturated fatty acids in photoreceptor membranes make the retina particularly prone to free radical damage and oxidative stress (Beatty et al., 2000). The RPE plays a crucial role in protecting the neural retina from oxidative stress by employing different antioxidant defense strategies. Melanin-containing granules within the RPE absorb excess light and scavenge light-induced free radicals (Wang et al., 2006). The RPE also contains antioxidant agents that further neutralize oxidative damage (Tate et al., 1993; Borras et al., 2019). Activation of autophagy helps to remove faulty cellular components generated by oxidative damage (Datta et al., 2017). In RP, rod photoreceptor death results in decreased oxygen consumption, creating a hyperoxic environment that may contribute to the progressive degeneration of cones (Shen et al., 2005). Notably, antioxidant treatments have been shown to reduce oxidative damage and delay cone death in an RP mouse model (Komeima et al. 2006, 2007). While no direct genetic link between RP and oxidative stress-related genes has been established, several studies warrant attention in this context. Mutations in the *ADIPOR1* gene have been associated with both syndromic (Xu et al., 2016) and non-syndromic dominant autosomal (Zhang et al., 2016) cases of RP. ADIPOR1 deficiency leads to reduced expression of DHA in photoreceptors (Osada et al., 2021). DHA, which plays an essential role in photoreceptor outer segment morphogenesis (SanGiovanni and Chew, 2005), is highly oxidative. Oxidative stress could cause lipid peroxidation of DHA in RPE, leading to RPE damage. Additionally, DHA is the precursor of neuroprotectin D1 (NPD1), which protects against RPE cell damage mediated by disease-induced accumulation of toxic components (Mukherjee et al., 2007), suggesting a link between AdipoR1 and oxidative stress defense defects. Furthermore, mutations in Ceramide kinase-like (CERKL) have been linked to non-syndromic autosomal recessive RP (Tuson et al., 2004; Avila-Fernandez et al., 2008). Recently, it was shown that CERKL is highly expressed in RPE cells and photoreceptors (Domènech et al., 2020). Though its exact function in RP pathogenesis is not fully understood, CERKL is thought to contribute to oxidative stress resistance (Tuson et al., 2004; Li et al., 2014). Reduced Cerkl expression leads to defects in RPE microvilli (Domènech et al.,

2020), as well as mitochondrial dysfunctions, including fragmentation, respiratory alterations, and polynucleation in RPE cells (García-Arroyo et al., 2021), accompanied by increased oxidative stress (García-Arroyo et al., 2023). Another RP-associated protein, Sema4A, has also been linked to protection against oxidative stress, in addition to its role in the retinoid cycle. In response to oxidative stress, Sema4A regulates the secretion of the lysosomal precursor protein prosaposin from the RPE, which supports photoreceptor survival (Toyofuku et al., 2012). Moreover, nuclear factor erythroid 2-related factor 2 (NRF2) is a transcription factor that regulates the expression of antioxidant proteins, playing a crucial role in protecting cells against oxidative damage (He et al., 2020). AAV-mediated overexpression of Nrf2 in the RPE rescued both the RPE and cones in the rd1 mouse model (Wu et al., 2021).

The RPE secretes various immunosuppressive factors, including the anti-inflammatory regulatory interleukins IL-10 (Idelson et al., 2018), interferon-gamma (IFN-gamma) (Kumar et al., 2004), and prostaglandin E2 (Sekiryu and Fujiwara, 1999). As a secretory epithelium, the RPE produces and secretes a range of growth factors, such as nerve growth factor (NGF) (Chakrabarti et al., 1990), transforming growth factor beta 1 and 2 (TGF-β1 and -β2) (Hirsch et al., 2015), pigment epithelium-derived factor (PEDF) (Zhu et al., 2011), and fibroblast growth factors (FGFs) (Seidler et al., 1999; Chinchore et al., 2017). Several of these survival factors have been explored as neuroprotective therapies to prevent photoreceptor degeneration. In vitro studies on adult retinal explants cultured with and without the RPE/choroid/sclera complex showed a reduction in FGF target gene expression in explants lacking the RPE/choroid/sclera complex (Chinchore et al., 2017). Additionally, administration of NGF slowed photoreceptor degeneration in the RP mouse model C3H (Lambiase and Aloe, 1996). More recently, RPE was found to produce and release insulin, influencing glucose metabolism in the retina and protecting it from starvation (Iker Etchegaray et al., 2023).

6. RPE-based treatments for RP

Despite significant advances in our understanding of RP through preclinical models, genetic studies, and elucidation of pathophysiological mechanisms, a curative treatment remains an unmet need. This is largely due to the genetic heterogeneity of RP, which makes it challenging to develop gene therapies that address all causative genes. To add up, RP patients experience variable clinical symptoms, which often go unnoticed for years before visual loss becomes apparent, creating a gap between disease onset and diagnosis (Kim et al., 2020; Holanda et al., 2024).

Over the past few decades, non-invasive high-resolution ophthalmic optical imaging technologies have significantly enhanced the diagnosis, monitoring, and understanding of ocular diseases. Spectral domain optical coherence tomography (SD-OCT) (Huang et al., 1991) has become the gold standard imaging modality in a wide range of retinal disorders, including RP (Oh et al., 2020; Ruggeri et al., 2024). SD-OCT has proven effective in tracking photoreceptor degeneration and assessing changes in the RPE-choriocapillaris layer (Jacobson et al., 1997; Yang et al., 2011). Advances in OCT technology have further improved the image resolution, enabling better evaluation of RPE thickness (Drexler et al., 2001; Götzinger et al., 2008), melanin density (Sakai et al., 2022), and RPE migration into the neural retina (Miura et al., 2017). However, SD-OCT is limited in its ability to detect structural changes at the cellular level (Scoles et al., 2013; Aumann et al., 2019). This limitation has been addressed with adaptive optics scanning light ophthalmoscopy (AOSLO), which allows in vivo imaging of the human RPE cell mosaic (Roorda et al., 2007; Morgan et al., 2009; Granger et al., 2018), and tracking of organelle motility within RPE cells (Liu et al., 2019).

Artificial intelligence (AI) approaches have been applied to ophthalmic imaging, particularly OCT, for diagnosis and disease management. Several AI tools have been developed to analyze OCT images, demonstrating high accuracy in detecting various retinal diseases (Kapoor et al., 2019; Ting et al., 2019). As OCT images offer a robust resource for assessing outer nuclear layer thickness—a surrogate for photoreceptor loss—numerous studies have used AI algorithms in RP to model disease progression and correlate retinal structure with visual function (Camino et al., 2018; Zhao et al., 2023; Eckardt et al., 2024). In addition to the recent progress in understanding RP pathomechanisms, including cellular targets and common molecular pathways, improvements in imaging techniques are instrumental not only for diagnosis but also for evaluating treatment efficacy. This is especially relevant given the promising pipeline of preclinical therapies advancing toward clinical translation.

Given the critical role of the RPE in maintaining photoreceptor integrity and homeostasis, there is a great interest in targeting the RPE as a novel therapeutic strategy. In this section, we review the current landscape of clinical trials for RP and the preclinical pipeline of potential therapies centered on the RPE, summarized in Table 3.

6.1. Gene therapy approaches

Currently, only a small subset of patients can benefit from individualized gene therapy. The first FDA-approved gene therapy for an inherited retinal disease, voretigene neparvovec-rzyl (Luxturna), became available in December 2017 for patients with confirmed biallelic *RPE65* mutation-associated inherited retinal disease (Hauswirth et al., 2008; Russell et al., 2017; Maguire et al., 2019). Two ongoing observational studies (Patient Registry) evaluate the real-world safety and effectiveness of Luxturna (NCT03597399, Spark Therapeutics, Inc. and NCT04983823, Baker Heart and Diabetes Institute). Clinical studies have demonstrated significant improvements using multiple functional and structural measures of the retina, with benefits maintained for up to 2-years post-treatment (Deng et al., 2022; Fischer et al., 2024). However, some patients developed progressive perifoveal chorioretinal atrophy following subretinal injection (Gange et al., 2022) and RPE atrophy with consequent photoreceptor loss, although functional outcomes remained stable (Reichel et al., 2023).

Beyond RPE65, several RPE-specific gene therapy approaches are being explored in preclinical and clinical studies. A phase I open-label study investigated rAAV2-VMD2-hMERTK in six patients with *MERTK*-related RP, administering two doses of the viral vector via subretinal injection. The ocular and systemic safety profiles were acceptable over a two-year follow-up period, but visual improvements were not sustained (Ghazi et al., 2016). A current phase II study (NCT03374657) is evaluating the safety and efficacy of CPK850 (scAAV8- RLBP1) in RP patients with mutations in the *RLBP1* gene.

6.2. Cell transplant approaches

Cell-based therapeutic strategies have added a new dimension in efforts to restore vision in degenerative retinopathies. The immune-privileged environment of the eye, where the BRB helps suppress immune responses, makes the subretinal space a safe and efficient target for cell transplantation-based therapies. RPE cells derived from human embryonic (hESCs) and human induced pluripotent stem cells (hiPSCs) are gaining particular interest as substrates for transplantation to prevent photoreceptor degeneration and preserve visual function. This is because RPE cells do not require extensive synaptic connections, unlike the stratified neural retina (Alexander et al., 2015). Additionally, the well-established protocols facilitate the production of high-quality, clinical-grade RPE cells in substantial quantities, ensuring reproducibility (West et al., 2020; Surendran et al., 2021; Wu et al., 2023). Three main surgical techniques have been employed to restore or bypass damaged RPE in different retinopathies: 1. surgical autologous transplantation of RPE as an intact cell sheet (RPE-choroid patch graft), 2. subretinal injection of RPE as a cell suspension, and 3. macular translocation, which involves repositioning the macula to an area with healthier RPE (Alexander et al., 2015; Zartasht Khan et al., 2022).

Table 3
Ongoing and completed clinical trials for RP, categorized by therapeutic approach, including gene therapy, cell transplantation, and pharmacological interventions.

Trial identifier	Type	Gene target	Method of administration	Clinical trial phase	Sponsor
Gene therapy					
NCT03374657	scAAV8- RLBP1 (CPK850)	RLBP1	Subretinal	Phase 1/2	Novartis Pharmaceuticals
NCT01482195	rAAV2-VMD2-hMERTK	MERTK	Subretinal	Phase 1	King Khaled Eye Specialist Hospital
Cell transplantation					
NCT03963154	hESC-derived RPE		Subretinal transplantation	Phase 1/2	Center d'Etude des Cellules Souches
NCT03566147	Human primary RPE cells		Subretinal transplantation	Phase 1	Eyecure Therapeutics Inc.
NCT03944239	hESC-derived RPE		Subretinal transplantation	Phase 1 Completed in 2021 without results	Qi Zhou
Drugs					
NCT01014052	QLT091001	RPE65 and LRAT	Oral	Phase 1	QLT Inc.
NCT05902962	VP-001	PRPF31	intravitreal	Phase 1	PYC Therapeutics

Seminal studies by (Li and Turner, 1988; Lavail et al., 1992) demonstrated that subretinal injection of RPE cells preserved the structure and function of photoreceptors in an RCS rat model. While preclinical RP animal studies (Surendran et al., 2021), and clinical outcomes of RPE transplants in age-related macular degeneration and Stargardt's macular dystrophy (Schwartz et al., 2015) have been positive, the clinical trial pipeline for RPE transplantation in RP patients remains limited. Currently, two registered clinical trials are evaluating the safety and tolerability of hESC-derived RPE transplantation in RP patients: A phase I/II open-label trial (NCT03963154) investigating patch transplantation of hESC-derived RPE in patients with monogenic RPE-specific mutations in *RPE65, LRAT and MERTK*, expected to be completed in 2026. A clinical trial (NCT03566147) involving subretinal transplantation of human primary RPE cells in RP and LCA patients, which has been completed, though the results have not yet been posted.

The urgent need for safe and effective RPE cell transplantation has driven increasing interest in clinical trials for RP. While different RPE transplantation approaches are available, significant challenges remain—particularly regarding the origin of RPE cells (iPSCs vs ESCs) and the transplantation method (cell suspension vs. sheet transplantation). iPSCs offer the advantage of being patient-specific, thereby reducing the risk of immune rejection. However, iPSCs can carry the patient's mutations, which contribute to disease processes and require gene editing before transplantation (Zartasht Khan et al., 2022), and their reprogramming from somatic cells remains a slow and complex process (Rohowetz and Koulen, 2023). On the other hand, ESCs can be efficiently differentiated into high-quality RPE cells, but they are not autologous and face ethical concerns. Additionally, ESC-derived RPE cells are not unlimited in supply, posing another logistical hurdle. Addressing these challenges will be crucial for optimizing RPE transplantation strategies and advancing clinical trials to provide long-term, effective treatments for RP patients.

6.3. Pharmacological approaches

An open-label proof-of-concept study (NCT01014052) evaluating a 7-day oral dose of 9-cis-retinyl acetate (QLT091001) demonstrated an acceptable safety profile and some improvements in visual field and/or visual acuity in most patients with RP caused by mutations in RPE65 or LRAT (Scholl et al., 2015). 9-cis-retinyl acetate, an artificial retinoid prodrug, increased rhodopsin regeneration and improved ERG responses in aged wild-type mice (Maeda et al., 2009). However, the short clinical study period (7 days) limits the ability to draw definitive conclusions, no follow-up studies have been conducted. Additionally, a Phase I/II repeat-dose, open-label, four-arm safety and efficacy study (NCT06852963) is underway to evaluate the safety and tolerability of two intravitreal doses of VP-001 in participants with confirmed PRPF31 mutation-associated RP (PYC Therapeutics). VP-001 is designed to enhance PRPF31 expression by downregulating CNOT3 activity. CNOT3 has been identified as a key modifier gene influencing the penetrance of PRPF31 mutations by suppressing PRPF31 expression (Venturini et al., 2012).

6.4. RPE: A shuttle for delivering drugs and genes to the retina

Recently (Jong et al., 2023), developed a novel approach utilizing iPSC-derived RPE cells to deliver exogenous soluble CX3CL1 (sCX3CL1). sCX3CL1 exerts neuroprotective effects by inhibiting microglia activation. Subretinal injection of AAV8-sCX3CL1 significantly prolonged cone survival in three RP mouse models, improving visual function. However, the authors were unable to demonstrate that sCX3CL1 overexpression directly inhibited microglia activation (Wang et al., 2019). Additionally, transgenic sCX3CL1-expressing hESCs, differentiated into hRPE cells, were subretinally transplanted into rd10 mice, successfully preventing photoreceptor degeneration in a localized manner. This strategy – using transplanted cells to deliver therapeutic genes – seems an attractive alternative to AAV-mediated gene therapy. A notable limitation of AAV vectors is their dose-dependent immune response, especially at high doses (Ertl, 2022), with the RPE being especially sensitive to viral toxicity (Xiong et al., 2019). Utilizing the RPE as a therapeutic shuttle could mitigate this issue. However, further studies are required to assess the long-term survival of hRPE in a xenogeneic host and to determine the durability of therapeutic effects from sCX3CL1-expressing hRPE, including potential improvements in visual function.

6.5. The fate of RPE after photoreceptor rescue

In vivo rescue experiments on preclinical mouse models provide valuable insight into the effects of therapeutic interventions, in particular gene therapy, not only on photoreceptor cells but also on other affected retinal cells. Several studies have focused on different aspects of retinal response, including photoreceptor morphology and function (Koch et al. 2015, 2017), inner retinal remodeling (Kajtna et al., 2022; Diaz-Lezama et al., 2023; Scalabrino et al., 2023) and metabolic changes (Ayten et al., 2024). The light-inducible TVRM4 mouse model exhibits structural alterations in tight junctions and functional impairment of the RPE barrier in response to photoreceptor degeneration (Napoli et al., 2021; Napoli and Strettoi, 2023). One month after light induction, when function was partially recovered (Gargini et al., 2017), tight junction alterations were also partially restored, suggesting that these changes are not irreversibly compromised if photoreceptor degeneration is mitigated (Napoli and Strettoi, 2023). However, another study using the *Pde6b*$^{STOP/STOP}$ RP mouse model found that RPE remodeling was not prevented by photoreceptor rescue at late disease stages (Kajtna et al., 2022). Further investigations are needed to understand the extent of RPE remodeling reversibility and how these outcomes can be integrated into therapeutic strategies.

7. Summary and future perspectives

Significant progress has been made in understanding the genetic architecture and the multiple underlying pathophysiological pathways of RP, driven by the development of preclinical models, including animal and in vitro cell models, as well as advances in single-cell RNA sequencing and omics technologies. The genetic heterogeneity of RP, combined with the influence of gene disease modifiers, underscores the complexity of its pathophysiology. The interaction network in the retina leads to degeneration of not only the mutant rod photoreceptors but also to remodeling of all other retinal cells. While the non-autonomous secondary cone degeneration has been investigated for decades, the secondary changes of the RPE have been mainly ignored. However, altered cell polarity and loss of junctional complexes in RPE cells, which compromise phagocytosis and the blood-retinal barrier, might contribute to the further pathogenesis of cone photoreceptor degeneration.

Although the metabolic interplay seems to be a key component of the retina-RPE symbiosis, our understanding of metabolic alterations within the RPE-photoreceptors ecosystem in RP remains limited. It is becoming more evident that the metabolic demands for photoreceptors vary depending on their physiological or pathological state. However, most of our current knowledge comes from isolated cell culture models, which do not recapitulate the complexity of this highly interdependent system. Further research on the metabolic remodeling during RP pathogenesis is essential, as it may uncover gene-independent therapeutic targets.

RPE cells have been therapeutically targeted through both gene therapy and transplantation approaches. The success of clinical trials involving RPE transplantation for disorders such as AMD and Stargardt (Schwartz et al., 2015; Li et al., 2021; Brant Fernandes et al., 2023; da Cruz et al., 2024) provides hope for the treatment of RP. However, the effectiveness of RPE transplantation may be limited to patients with minimal photoreceptor degeneration (Somasundaran et al., 2020). Multimodal approaches could be considered to target photoreceptors and RPE together.

These findings suggest that RPE and photoreceptors are a symbiotic functional unit, requiring sophisticated collaboration to maintain retinal homeostasis.

CRediT authorship contribution statement

Hanaa Ghanawi: Writing – review & editing, Writing – original draft, Investigation, Data curation, Conceptualization. **Susanne F. Koch:** Writing – review & editing, Writing – original draft, Supervision, Resources, Data curation, Conceptualization.

Contents

- Molecular, structural, and functional changes in the RPE associated with RP, based on findings from preclinical models and patient studies.
- How mutations in RPE-specific genes contribute to key pathological mechanisms in RP, including disruptions in the visual cycle, phagocytosis, metabolism, RNA processing, and structural support.
- Recent therapeutic advances targeting the RPE for RP treatment, including gene therapy, RPE cell transplantation, and pharmacological interventions.

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Declaration of interest statement

We have nothing to declare.

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Abbreviations

AdipoR1 - Adiponectin Receptor 1
AMD - Age-Related Macular Degeneration
AOSLO - Adaptive Optics Scanning Light Ophthalmoscopy
AI - Artificial Intelligence
BRB - Blood-Retinal Barrier
CERKL - CERamide Kinase Like
CLC-2 - Chloride Channel Protein 2
CRALBP - Cellular Retinaldehyde–Binding Protein
CRB1 - Crumbs homolog 1
DHA - Docosahexaenoic Acid
Dnmt1 DNA methyltransferase 1
EMMPRIN - Extracellular Matrix Metalloproteinase Inducer
EMT - Epithelial-Mesenchymal Transition
ES - Embryonic Stem Cells
FAK - Focal Adhesion Kinase
FGF - Fibroblast Growth Factor
HK2 - Hexokinase 2
IFN-gamma - Interferon-gamma
IL-10 - Interleukin-10
iPS induced Pluripotent Stem Cells
JAMs - Junctional Adhesion Molecules
LCA - Leber congenital amaurosis
LDHA - Lactate Dehydrogenase
LRAT - Lecithin Retinol Acyltransferase
MARVEL - Mal and related proteins for vesicle trafficking and membrane link
MCT - Monocarboxylate Transporter
Mertk - Mer Tyrosine Kinase
MFG-E8 - Milk Fat Globule-EGF Factor 8
N-CAM - Neural cell adhesion molecule
NGF - Nerve Growth Factor
NPD1 - Neuroprotectin D1
NRF2 - Nuclear factor erythroid 2-related factor 2
OS – Outer segment
PEDF - Pigment Epithelium-Derived Factor
PKM2 - Pyruvate Kinase M2
PRPFs - Pre-mRNA Processing Factors
PS - Phosphatidylserine
PVR - Proliferative Vitreoretinopathy
RDH - Retinol Dehydrogenase
RBP3 - Retinol-Binding Protein 3
RGR - Retinal G-Protein-Coupled Receptor
ROS Reactive Oxygen Species
RP - Retinitis Pigmentosa
RPE - Retinal Pigmented Epithelium
Sema4A - Semaphorin 4A
STGD1 - Stargardt disease-1
TEER - Transepithelial Electrical Resistance
TEM – Transmission Electron microscopy
TGF-β1 and -β2 - Transforming Growth Factor Beta 1 and 2
VEGF-A - Vascular Endothelial Growth Factor-A
ZO - Zonula Occludens

Data availability

Data will be made available on request.

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