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Review

Photoreceptor Susceptibility to Ferroptosis: Membrane Lipids, Mitochondria, and Retinal Pigment Epithelium–Photoreceptor Coupling

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Abstract

Photoreceptor (PR) degeneration is a shared pathological feature of multiple blinding retinal diseases. This review examines the mechanisms underlying PR vulnerability to lipid-peroxidation-driven injury, with emphasis on three interconnected features: the marked enrichment of docosahexaenoic acid (DHA) and other polyunsaturated fatty acids (PUFAs) in PR outer-segment disc membranes; the chronically high metabolic demand of PRs and the specialized spatial organization of their mitochondria; and retinal pigment epithelium (RPE)–PR metabolic coupling, including outer-segment renewal and phagocytic turnover, glucose transport and lactate shuttling, and the visual cycle. We also summarize antioxidant defense systems centered on the cystine/glutamate antiporter (xCT)–glutathione (GSH)–glutathione peroxidase 4 (GPX4) axis and mitochondrial GPX4 (mtGPX4), which restrict iron-dependent lipid peroxidation in PRs. We propose that highly oxidizable membrane lipid substrates, mitochondrial homeostatic imbalance, and impaired RPE–PR metabolic coupling may collectively shape PR susceptibility to ferroptosis-associated injury. From a therapeutic perspective, this framework supports multitarget strategies designed to interrupt lipid-peroxidation propagation, stabilize mitochondrial redox homeostasis and quality-control mechanisms, and restore RPE–PR metabolic support and local iron-buffering capacity.

Keywords: photoreceptors; ferroptosis; lipid peroxidation; mitochondrial homeostasis; retinal pigment epithelium; RPE–PR coupling; polyunsaturated fatty acids

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1. Introduction

Progressive photoreceptor (PR) injury and loss constitute a major pathological basis for irreversible visual dysfunction in many blinding retinal diseases. Age-related macular degeneration (AMD) is one of the leading causes of blindness among older adults [1]. In 2021, approximately 8.06 million people worldwide were affected by AMD-related visual impairment, and this number is projected to rise to 21.34 million by 2050 [2]. In advanced AMD, outer-retinal atrophy or neovascular exudation is associated with photoreceptor degeneration and central vision loss, leading to marked impairment of quality of life [3]. Retinitis pigmentosa (RP) is a common inherited retinal degenerative disease with a global prevalence of approximately 1 in 5,000 [4]. Despite its marked genetic heterogeneity [5], progressive PR degeneration remains a central pathological hallmark of RP [6]. Diabetic retinopathy (DR), a major ocular complication of diabetes, is projected to affect approximately 161 million people worldwide by 2045 [7].

Beyond classic microvascular abnormalities, accumulating evidence indicates that DR is also accompanied by early neuroretinal injury, in which PR dysfunction may precede overt microvascular lesions and further contribute to disease progression [8,9]. Importantly, DR remains clinically defined and staged mainly by vascular manifestations, whereas early diabetic retinal neurodegeneration may

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represent an additional and potentially independent target for intervention [10]. In this context, current therapeutic strategies remain largely focused on vascular complications, exudative disease activity, or specific disease stages. For example, intravitreal anti-vascular endothelial growth factor (VEGF) therapy is a first-line treatment for neovascular, exudative AMD; however, it primarily suppresses VEGF-driven neovascular leakage and does not directly target the upstream degenerative mechanisms that contribute to PR loss in non-exudative or early-stage AMD [3,11].

Similarly, broadly effective therapies that delay or halt PR degeneration in RP remain limited [12]. Therefore, elucidating the molecular basis of PR degeneration, particularly the upstream mechanisms that determine PR susceptibility to injury, is crucial for developing novel neuroprotective strategies. Since ferroptosis was first defined in 2012 [13], this iron-dependent, lipid-peroxidation-driven form of cell death has been increasingly implicated in the onset and progression of multiple retinal diseases, including AMD, RP, and DR [14]. Studies in PR-related models have shown that solute carrier family 7 member 11 (SLC7A11) downregulation weakens antioxidant defense and exacerbates ferroptosis-associated injury [15]. In diabetic models, iron burden and lipid peroxidation accompany PR injury; in inherited degeneration models, ferroptosis/oxytosis-related pathways have also been implicated [16,17]. Impaired all-trans-retinal (atRAL) clearance likewise induces Fe^{2+} accumulation, glutathione (GSH) depletion, and amplification of membrane lipid peroxidation [18]. Collectively, these findings suggest that ferroptosis may represent an important mechanism linking metabolic imbalance, oxidative stress, and PR degeneration. However, apoptosis remains the most extensively studied mode of PR death, and direct PR-specific evidence for ferroptosis, well as clearer mechanistic stratification, is still needed [19]. In PR-like 661W cells and other retinal neuronal injury models, interventions that reduce ferroptosis-related changes have shown protective effects [20,21].

These observations raise the question of why PRs are particularly susceptible to lipid peroxidation under stress conditions. Several distinctive structural and metabolic features may help explain this susceptibility. First, PR outer-segment disc membranes are among the retinal membrane structures most highly enriched in docosahexaenoic acid (DHA) and other polyunsaturated fatty acids (PUFAs). This specialized lipid composition is essential for phototransduction, membrane fluidity, and disc renewal [22,23], but it also provides abundant substrates for lipid-peroxidation chain reactions [24,25]. Second, PRs are among the most metabolically demanding neurons in the retina, and cone-enriched regions, including the macula, show greater pyruvate metabolism and tricarboxylic acid cycle activity [26]. At the same time, the dense and highly ordered mitochondrial populations within the PR inner segment, particularly in the cone ellipsoid region, indicate that mitochondria not only support energy conversion but also help maintain photoreceptor structure and optical function [27,28].

Recent ultrastructural studies of human rod photoreceptors further reveal a specialized inner-segment architecture with distinctive mitochondrial positioning, suggesting that PR mitochondrial architecture is highly specialized and may vary across photoreceptor subtypes [29]. Although this sustained, high-flux, highly organized state supports visual signal transduction, it also suggests that, when mitochondrial dynamics, quality control, iron handling, or membrane homeostasis are disturbed, PRs may become particularly vulnerable to the accumulation of mitochondrial reactive oxygen species (mtROS), mitochondrial membrane-potential dysregulation, and lipid peroxidation. Third, PRs reside within an outer-retinal metabolic microenvironment shaped by the retinal pigment epithelium (RPE) [30]. The RPE mediates the phagocytosis, degradation, and partial lipid recycling of photoreceptor outer segments (POS) [31,32].

Through its functions in the visual cycle and outer-retinal retinoid metabolism, the RPE also promotes atRAL clearance and helps limit related toxic stress, thereby maintaining local homeostasis [33]. When post-phagocytic POS processing is impaired, substrate allocation becomes imbalanced, or retinoid metabolism is disrupted, lipid-peroxidation-related and ferroptosis-promoting stress may accumulate within the RPE–PR metabolic unit and be further amplified [18]. Against this background, the cystine/glutamate antiporter (xCT)–GSH–glutathione peroxidase 4 (GPX4) axis

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constitutes the core molecular defense against iron-dependent lipid peroxidation [34–36]. Mitochondrial GPX4 (mtGPX4), in particular, is critical for limiting the accumulation of mitochondria-associated peroxidized phospholipids and for maintaining homeostasis in PUFA-enriched membrane systems [37,38].

From this perspective, PR vulnerability to ferroptosis is better understood not simply as the consequence of an isolated cell-death pathway but as a vulnerability state shaped by highly oxidizable membrane lipid substrates, a chronically high-demand mitochondrial state, and the RPE–PR metabolic microenvironment. This review outlines the membrane lipid, mitochondrial, and RPE–PR coupling mechanisms underlying PR vulnerability to ferroptosis. It then summarizes the core defense pathways, including the xCT–GSH–GPX4 axis and mtGPX4, and discusses how disturbances in mitochondrial dynamics, quality control, biogenesis, and iron homeostasis may increase PR susceptibility to ferroptosis-associated injury. The review also considers how an imbalance in RPE–PR metabolic coupling can trigger and amplify ferroptosis-associated stress, and evaluates potential interventions to reduce PR vulnerability in AMD, RP, DR, and other blinding retinal diseases.

2. Biological Basis of Photoreceptor Susceptibility to Ferroptosis

2.1. Lipid Basis

PR outer-segment disc membranes have a highly specialized lipid composition; they are among the most highly polyunsaturated biological membrane structures in the retina and are particularly enriched in DHA [22]. This lipid specialization is essential for maintaining the architecture of outer-segment disc membranes and PR homeostasis. Mechanistically, the lipid composition of PR outer-segment membranes is established through the coordinated regulation of fatty acid supply, selective esterification, and phospholipid remodeling. Acyl-CoA synthetase long-chain family member 6 (ACSL6) supports DHA enrichment and retention in retinal membrane phospholipids and is critical for shaping the phospholipid composition of rod photoreceptors; *Acsl6* inactivation markedly reduces DHA-containing retinal phospholipids and leads to progressive rod photoreceptor loss [39].

Multifunctional protein 2 (MFP2) deficiency causes DHA insufficiency and early degenerative changes in both PRs and the RPE, supporting a role for peroxisomal β-oxidation in maintaining retinal DHA availability and outer-retinal integrity [40]. Likewise, loss of lysophosphatidic acid acyltransferase 3 (LPAAT3) reduces DHA levels in retinal membrane phospholipids, disrupts PR outer-segment disc organization, and impairs visual function [41]. Together, these findings indicate that DHA is required not only for shaping membrane composition but also for maintaining disc membrane ultrastructure. Accordingly, lipid homeostasis in PR outer-segment membranes depends on the coordinated action of multiple pathways that govern lipid metabolism and membrane organization.

Notably, the burden of oxidizable membrane lipid substrates also differs among PR subtypes. Compared with cone-dominant samples, rod-dominant samples contain higher levels of PUFAs, including long-chain and very-long-chain polyunsaturated fatty acids (LC- and VLC-PUFAs), suggesting intrinsic subtype-specific differences in the substrates available for peroxidation [24]. At the molecular level, DHA-containing phospholipids stabilize rhodopsin conformation through specific molecular interactions [23]. Although this membrane specialization supports visual function, it also renders outer-segment disc membranes chemically more vulnerable to oxidative attack. The outer retina is continuously exposed to light and resides in an oxygen-rich environment, where PUFAs are particularly susceptible to reactive oxygen species (ROS)-mediated lipid-peroxidation chain reactions because of their multiple double bonds [25]. Collectively, these features create a highly PUFA-enriched, substrate-rich membrane environment that permissive for lipid peroxidation in PR outer segments.

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2.2. Mitochondrial Basis

PRs are major contributors to the high energy demand of the outer retina and require substantial adenosine triphosphate (ATP) to support dark-current-associated ion transport, phototransduction-related homeostasis, and synaptic transmission [42,43]. Despite their pronounced aerobic glycolytic phenotype, PRs remain highly dependent on mitochondrial metabolism. Metabolomic studies show that, compared with rod-enriched regions, cone-enriched retinal regions, particularly the macula, exhibit greater pyruvate metabolism, tricarboxylic acid cycle activity, and lipid synthesis [26], indicating higher demands for mitochondrial oxidative metabolism and biosynthetic support in cone-dominant retinal regions. Consistent with this, loss of glutamic-oxaloacetic transaminase 1 (GOT1) disrupts cytosolic–mitochondrial metabolic coupling and leads to PR degeneration [44], underscoring the importance of intact mitochondrial metabolism for PR homeostasis.

Beyond their high metabolic demands, PR mitochondria also exhibit a spatial organization closely aligned with cellular function. Recent studies of human rod photoreceptors have identified an accessory inner segment that lies adjacent to the outer segment and extends along its lateral aspect, with mitochondria positioned at the base of this accessory structure [29]. In cone photoreceptors, mitochondria are densely concentrated within the ellipsoid region of the inner segment, where they form highly ordered bundles immediately adjacent to the base of the outer segment; this organization has been proposed to facilitate local light focusing and guide incident light, thereby enhancing photon delivery to the outer segments [27]. Three-dimensional reconstructions of primate photoreceptors further demonstrate that inner-segment mitochondria exhibit a dense and highly ordered spatial arrangement, a configuration consistent with the high bioenergetic demands and specialized functional architecture of PRs [28].

Moreover, optic atrophy 1 (OPA1) has been linked to the orderly spatial alignment of neighboring PR mitochondria [45], suggesting that the maintenance of this specialized organization depends, at least in part, on mitochondrial dynamics. Taken together, PR mitochondria function under sustained high metabolic flux within a highly ordered spatial architecture. These features underscore the dependence of PRs on intact mitochondrial homeostasis. When mitochondrial homeostasis is disrupted, PRs may become more vulnerable to redox imbalance and mitochondrial dysfunction, thereby increasing their susceptibility to lipid peroxidation- and ferroptosis-associated injury.

2.3. RPE–PR Metabolic Coupling

PRs reside at the outer-retinal interface, where the RPE, Bruch's membrane, and the choroid form a tightly coupled structural and metabolic unit. Within this interface, the apical–basal polarity of the RPE determines nutrient influx, metabolite efflux, and outer-segment turnover, thereby providing the structural basis for metabolic homeostasis in the outer retina [30]. Under physiological conditions, new discs are generated at the base of the outer segment, whereas aged discs are shed from the distal tip and phagocytosed by the RPE. The RPE mediates the recognition, phagocytosis, and lysosomal degradation of POS and contributes to partial lipid recycling [31,32]. Outer-segment phagocytosis and processing are also closely linked to circadian regulation in the RPE [46].

After POS uptake, post-phagocytic degradation in the RPE is associated with fatty-acid release and β-hydroxybutyrate release from phagocytic RPE cells, suggesting that outer-segment processing is linked to lipid-derived substrate handling and metabolic adaptation in the RPE [47]. Defective RPE mitochondrial energetics and impaired oxidative metabolic programs may further disrupt RPE metabolic homeostasis in the context of outer-retinal disease [48]. Moreover, RPE phagocytosis can promote local insulin production and influence retinal glucose uptake and homeostasis, further indicating that POS turnover actively participates in the outer-retinal metabolic ecosystem [49]. Thus, RPE–PR coupling involves both disc clearance and post-phagocytic substrate handling in the RPE, thereby contributing to a continuous system of lipid turnover and substrate reallocation in the outer retina [50].

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Recent in vivo tracing evidence supports a model in which PRs consume glucose and export lactate to the RPE, where lactate may be catabolized; however, the quantitative contribution of lactate to RPE oxidative metabolism across species and disease stages remains to be further defined [51–53]. Together, glucose transfer and lactate handling contribute to a transcellular division of metabolic labor that supports outer-retinal homeostasis. The structural and metabolic organization of the RPE–PR unit is summarized in Figure 1. However, glucose is not merely an energy source for PRs. It also provides carbon skeletons for outer-segment renewal and related biosynthetic processes, and restricted glucose uptake leads to defective outer-segment renewal and shortening of rod outer segments [54,55].

In addition, glucose utilization in PRs depends on the maintenance of specific metabolic programs. Glycolysis sustained by pyruvate kinase M2 (PKM2) and hexokinase 2 (HK2) supports central carbon flux and helps maintain PR structural integrity, function, and long-term survival [56–59]. More broadly, recent reviews emphasize that metabolic regulation is central to PR survival, development, and repair [60]. At the transport level, the monocarboxylate transporter 1 (MCT1) and monocarboxylate transporter 3 (MCT3), together with their shared chaperone basigin (BSG), mediate lactate transport across the RPE–PR interface; disruption of this pathway perturbs outer-retinal metabolic homeostasis and compromises PR function [61]. Beyond nutrient exchange, the RPE is also essential for the visual cycle. Retinal pigment epithelium-specific 65-kDa protein (RPE65) participates in the regeneration of 11-cis-retinoids and is therefore critical for visual pigment renewal and sustained photosensitivity [33]. Collectively, the RPE and PRs are metabolically coupled through continuous outer-segment lipid turnover, energy-substrate exchange, and the metabolism and transport of visual-cycle-related retinoids. Together, these processes sustain outer-retinal homeostasis.

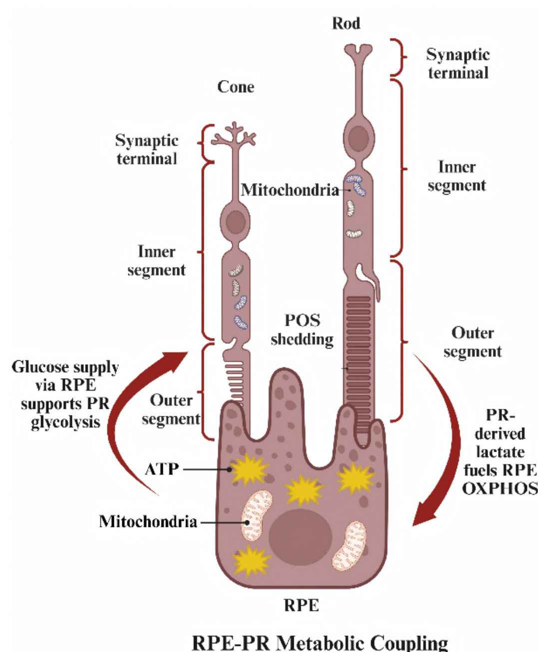

Figure 1. Structural organization of photoreceptors and metabolic coupling within the RPE–PR unit as a basis for photoreceptor ferroptosis susceptibility.

3. Antioxidant and Lipid-Redox Defense Systems Against Ferroptosis

3.1. xCT–GSH–GPX4 Axis-Mediated Antioxidant Defense in Photoreceptor Ferroptosis

The cystine/glutamate antiporter system xc$^-$, composed of the light-chain transporter subunit SLC7A11 and the heavy-chain subunit solute carrier family 3 member 2 (SLC3A2), mediates cystine

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uptake in exchange for glutamate export and thereby supports cysteine availability for GSH biosynthesis [34]. After entering the cell, cystine is reduced to cysteine and incorporated into GSH, which supplies reducing equivalents for GPX4-dependent lipid peroxide detoxification. GPX4 directly reduces phospholipid hydroperoxides in biological membranes to their corresponding lipid alcohols, thereby limiting the propagation of lipid-peroxidation chain reactions and suppressing ferroptosis [62,63]. Thus, either reduced cystine supply or impaired GPX4 activity weakens the cellular defense against iron-dependent lipid peroxidation and increases susceptibility to ferroptosis.

xCT deficiency alters local cysteine/GSH homeostasis in the retina and is associated with redox imbalance and altered mitochondrial activity, indicating that this transport system plays an important role in maintaining local antioxidant homeostasis in retinal tissue [64]. In PR-like 661W cell models, sodium iodate ($NaIO_3$) treatment is associated with decreased SLC7A11 expression, GSH depletion, elevated Fe^{2+} levels, ROS accumulation, and increased lipid peroxidation; exogenous GSH, Ferrostatin-1 (Fer-1), and N-acetylcysteine (NAC) alleviate $NaIO_3$-induced cell death and ferroptosis-associated phenotypes, suggesting that disruption of xCT–GSH-dependent antioxidant defense contributes to ferroptosis-associated injury in PR-like cells [65].

In high-glucose-treated 661W cells and diabetic mouse retinas, downregulation of SLC7A11 and GPX4 is accompanied by an increased iron burden and elevated ROS and malondialdehyde (MDA) levels, whereas Fer-1 partially reverses these changes [16]. These findings suggest that impairment of the xCT–GSH–GPX4 axis may also contribute to PR injury in diabetic retinopathy. More recent studies further indicate that SLC7A11 downregulation weakens antioxidant defense and aggravates ferroptosis-associated injury in PR-related models, reinforcing the view that SLC7A11 is a critical determinant of the integrity of the xCT–GSH–GPX4 axis [15]. In the rd10 model of inherited PR degeneration, ferroptosis-related genes are upregulated, and ferroptosis inhibitors partially improve visual function, supporting a role for ferroptosis-related pathways in inherited PR degeneration [17]. Beyond the canonical xCT–GSH–GPX4 axis, upstream regulators may also shape PR susceptibility to ferroptosis by affecting the stability of this pathway.

Studies have shown that cullin 7 (CUL7) downregulation reduces ubiquitin-mediated GPX4 degradation and attenuates ferroptosis-associated PR injury [66]. In light-damage models, lipocalin-2 (LCN2) inhibition is associated with reduced Fe^{2+} and MDA levels, restored SLC7A11 and GPX4 expression, and attenuated ferroptosis-associated injury in PRs [67]. Overall, current evidence supports the xCT–GSH–GPX4 axis as a core molecular defense against iron-dependent lipid peroxidation in PRs. When this axis is disrupted, PR vulnerability to ferroptosis-associated injury may increase substantially.

3.2. mtGPX4-Mediated Mitochondrial Lipid-Redox Defense in Photoreceptors

GPX4 is essential for preserving the integrity of PR membrane systems and subcellular architecture. Ueta et al. reported that GPX4 was abundantly expressed in PR inner segments and colocalized with mitochondrial markers; in mice with PR-specific deletion of *Gpx4*, PRs still differentiated into rods and cones but rapidly developed outer-segment disorganization, shortened connecting cilia, and mitochondrial structural abnormalities [37]. Azuma et al. further showed that mtGPX4 deficiency caused marked retinal accumulation of peroxidation products derived from DHA-containing phosphatidylethanolamine (PE), leading to cone loss before maturation and gradual rod degeneration after maturation, ultimately producing a cone–rod dystrophy-like phenotype [38]. Together, these findings indicate that mtGPX4 provides more than general antioxidant protection. It is also critical for limiting the accumulation of mitochondria-associated peroxidized phospholipids and for maintaining redox homeostasis in membrane systems enriched in PUFAs.

To date, direct evidence for upstream regulation of mtGPX4 in PRs remains limited. Studies in PC12 and HT22 neuronal models suggest that sirtuin 3 (SIRT3) activation may help protect against neuronal ferroptosis by reducing mtGPX4 acetylation [68]. In the retina, Ban et al. reported that SIRT3 deficiency was associated with mitochondrial abnormalities in PR inner segments and aggravated PR injury after light-induced stress [69]. However, direct evidence that SIRT3 regulates PR ferroptosis

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through mtGPX4 remains lacking. Taken together, these findings indicate that mtGPX4 is a mitochondrial antioxidant enzyme that directly limits mitochondria-associated phospholipid peroxides, thereby linking mitochondrial redox homeostasis to the integrity of PR membrane structures. Accordingly, when mtGPX4 function is impaired, mitochondrial phospholipid peroxides accumulate, thereby increasing PR susceptibility to iron-dependent lipid-peroxidation-driven injury.

3.3. Putative CoQ- and BH_4-Dependent Ferroptosis Defense Pathways in Photoreceptors

In addition to the canonical xCT–GSH–GPX4 axis and mtGPX4, the dihydroorotate dehydrogenase (DHODH)–reduced coenzyme Q ($CoQH_2$), ferroptosis suppressor protein 1 (FSP1)–coenzyme Q_{10} (CoQ_{10}), and GTP cyclohydrolase 1 (GCH1)–tetrahydrobiopterin (BH_4) systems have also been proposed as parallel or supplementary antiferroptotic defense pathways. However, direct evidence for these pathways in the retina, particularly in PRs, remains limited. DHODH is localized to the inner mitochondrial membrane and uses coenzyme Q (CoQ) as an electron acceptor during de novo pyrimidine synthesis, thereby generating the reduced form, $CoQH_2$ [70,71]. When GPX4 is inhibited, DHODH can limit mitochondrial membrane lipid peroxidation and suppress ferroptosis, suggesting that it acts partly in parallel with, and in cooperation with, mitochondrial GPX4 [72]. In studies of ocular tissues, however, direct evidence for a ferroptosis-suppressive role of DHODH remains scarce, and current data come mainly from hypoxia-stressed human corneal epithelial cell models [73].

Therefore, whether the DHODH–$CoQH_2$ system functions as an effective mitochondrial antiferroptotic defense in PRs remains unresolved. FSP1 uses nicotinamide adenine dinucleotide phosphate (NADPH) to reduce CoQ_{10} to ubiquinol, its reduced antioxidant form, thereby establishing a relatively GPX4-independent lipid radical-scavenging system [74,75]. In RPE-focused retinal studies, Yang et al. found that impaired FSP1 function exacerbated lipid peroxidation and RPE cell injury, whereas FSP1 overexpression protected RPE cells from sodium iodate-induced injury and attenuated ferroptosis-associated changes [76]. These findings suggest that the FSP1–CoQ_{10} system may participate in adaptive defense against lipid peroxidation in retinal cells, although its role in PRs remains to be clarified.

The GCH1–BH_4 system is thought to suppress ferroptosis through a mechanism that is relatively independent of the GSH–GPX4 axis by maintaining BH_4 levels and promoting lipid remodeling, thereby selectively preventing the depletion of peroxidation-prone PUFA-containing phospholipids [77]. In models of ischemic retinopathy, BH_4 precursor supplementation improves redox status and reduces apoptotic cell death mainly in the inner neural retina, but this does not yet establish a direct PR-specific antiferroptotic role for the GCH1–BH_4 system [78]. These core and putative antiferroptotic pathways are summarized schematically in Figure 2.

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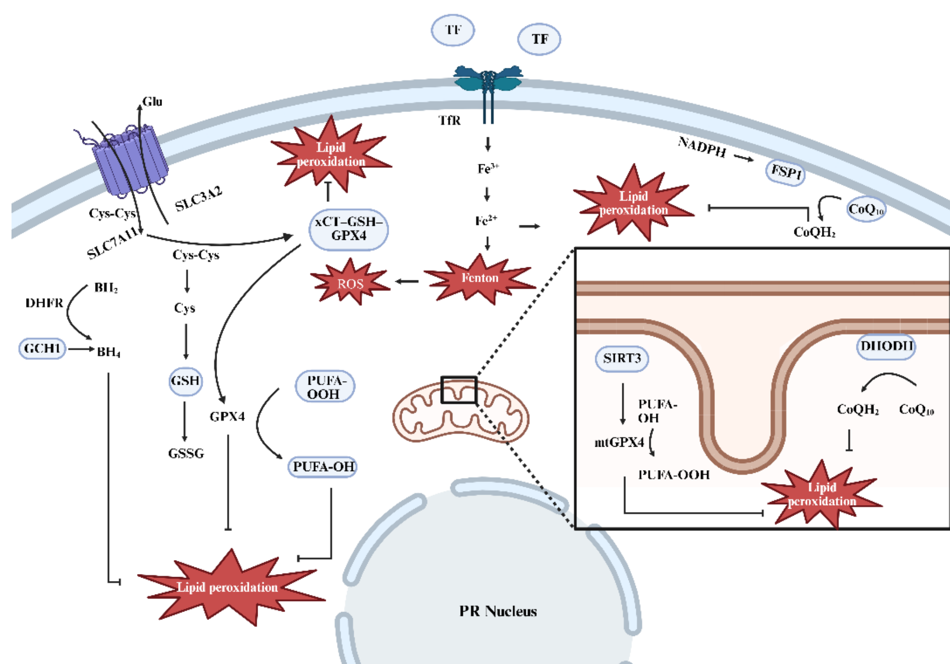

Figure 2. Core and putative ferroptosis-regulatory pathways relevant to photoreceptors.

4. Mitochondrial Homeostasis as a Determinant of PR Susceptibility to Ferroptosis

4.1. Imbalance in Mitochondrial Dynamics

4.1.1. Impaired Mitochondrial Fusion

Available evidence indicates that mitochondrial fusion contributes to the establishment of the specialized mitochondrial architecture and associated metabolic phenotype of rod photoreceptors [79]. Among the regulators involved in mitochondrial fusion, OPA1 is a key determinant of structural homeostasis in PR mitochondria. OPA1 mediates inner mitochondrial membrane fusion and cristae remodeling [80], and its loss in PR models leads to mitochondrial enlargement and disrupts the orderly alignment of adjacent mitochondria within the inner segment [45]. These findings indicate that OPA1 is closely linked to both the spatial organization of PR mitochondria and the structural stability of the inner mitochondrial membrane. Accordingly, OPA1 dysfunction may induce abnormal mitochondrial morphology and inner membrane disorganization, thereby potentially weakening the ability of PRs to adapt to metabolic and oxidative stress and increasing PR vulnerability to lipid-peroxidation-associated injury.

In addition to OPA1, mitofusin 2 (MFN2)-dependent maintenance of mitochondria–endoplasmic reticulum contact sites (MERCs) may represent another convergence point between impaired mitochondrial fusion and oxidative damage. Studies have shown that MFN2 dysfunction disrupts the structure and function of MERCs and impairs mitochondrial Ca^{2+} uptake through the inositol 1,4,5-trisphosphate receptor (IP3R) type 3 (IP3R3)–glucose-regulated protein 75 (GRP75)–voltage-dependent anion channel 1 (VDAC1) complex [81]. Evidence from other cell systems further suggests that MERC abnormalities can disrupt Ca^{2+} transport, alter ROS levels, and disturb ferroptosis-related lipid homeostasis [82]. In PR-related studies, IP3R type 2 (IP3R2)-mediated MERC-associated Ca^{2+} transport contributes to hypoxia-induced PR injury and is accompanied by mitochondrial dysfunction and increased cell death [83].

Related studies in SH-SY5Y neuroblastoma cells show that GPX4 inhibition promotes IP3R-mediated Ca^{2+} release, elevates mitochondrial Ca^{2+} levels, and drives ferroptosis [84]. Together, these

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findings suggest that impaired mitochondrial fusion may compromise PR resistance to oxidative stress by altering mitochondrial morphology and inner membrane structure, as well as by disrupting MERC-associated Ca^{2+} homeostasis and redox balance.

4.1.2. Aberrant Mitochondrial Fission

Enhanced dynamin-related protein 1 (DRP1)-dependent mitochondrial fission may increase PR susceptibility to lipid-peroxidation associated injury. In NIH-3T3 and HT-1080 cells, human NSCLC H441/A549 cells, Drp1fl/fl MEFs, and immortalized mouse hippocampal HT22 neurons, DRP1 activation or loss-of-function studies link ferroptosis induction to mitochondrial fragmentation, loss of membrane potential, and aggravated oxidative damage; conversely, DRP1 deficiency or deletion can partially delay these changes and preserve mitochondrial redox homeostasis [85,86]. Mechanistically, recent evidence indicates that mitochondrial fission is induced during ferroptosis and that disruption of mitochondrial dynamics, including interference with DRP1-dependent fission, can attenuate ferroptotic cell death, supporting a functional link between mitochondrial fission and ferroptosis-associated mitochondrial injury [87].

In retinal models, retinas from models of type 1 diabetes mellitus without overt diabetic retinopathy (T1DM-NDR), as well as high-glucose-treated 661W cells, exhibit increased DRP1 expression and phosphorylation, together with mitochondrial fragmentation, cristae disruption, reduced mitochondrial network branching, and loss of mitochondrial membrane potential [88]. Collectively, these findings suggest that excessive DRP1 activation impairs mitochondrial ultrastructural and functional homeostasis in PR-related models, aggravates oxidative injury, and thereby increases susceptibility to ferroptosis-associated damage. Evidence from outer-retinal cells further supports this view. Studies of RPE cells derived from donors with age-related macular degeneration (AMD) reveal disease-specific differences in mitochondrial fission and mitophagy responses, together with delayed recovery after stress, suggesting impaired restoration of mitochondrial homeostasis in outer-retinal cells [89].

Notably, the consequences of aberrant mitochondrial fission in PRs may extend beyond organelle-level energy imbalance and oxidative injury to include amplification of inflammatory signaling. In tumor cells models, mitochondria-localized cyclic GMP–AMP synthase (cGAS) has been shown to promote DRP1 oligomerization and suppress ferroptosis-related mitochondrial ROS accumulation [90]. Although this cGAS–DRP1 mechanism has not been directly demonstrated in PRs, retinal studies indicate that oxidative stress can activate cGAS–stimulator of interferon genes (STING) signaling in degenerating retinas, accompanied by cytosolic leakage of damaged DNA from PRs, and that inhibition of this pathway attenuates retinal inflammation and PR degeneration [91]. Consistently, cGAS-dependent inflammatory activation has been linked to DNA-induced microglial activation and PR degeneration in retinal degeneration models [92]. Therefore, aberrant mitochondrial fission may directly disrupt mitochondrial homeostasis and may also exacerbate cellular injury by amplifying inflammatory signaling.

4.2. Insufficient Mitochondrial Quality Control

The PTEN-induced kinase 1 (PINK1)–Parkin pathway is a canonical mechanism of mitochondrial quality control. Loss of mitochondrial membrane potential activates PINK1/Parkin-dependent ubiquitin signaling on the outer mitochondrial membrane, thereby marking damaged mitochondria for autophagy–lysosomal clearance through the recruitment of autophagy adaptors [93,94]. Retinal studies suggest that selective mitochondrial clearance is an integral component of retinal development and remodeling. Two peaks of mitophagy have been observed during retinal development; the second is PINK1/Parkin-dependent and follows an increase in oxidative stress [95]. This finding indicates that the retina possesses an active mitochondrial quality-control program. By facilitating the recognition and clearance of damaged mitochondria while limiting their abnormal persistence, mitophagy serves as an important physiological mechanism for maintaining the homeostasis of the mitochondrial pool.

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Consistent with this, PR-related cellular models further suggest that oxidative stress activates PINK1/Parkin-associated mitochondrial quality control. In H_2O_2-treated 661W cells, mitophagy is accompanied by increased colocalization of PINK1 with Parkin and of microtubule-associated protein 1 light chain 3 (LC3) with mitochondria [96]. In peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α)/nuclear factor erythroid 2-related factor 2 (NRF2; encoded by *NFE2L2*)-deficient models, RPE cells show elevated light chain 3 beta (LC3B), PINK1, and Parkin levels without a corresponding increase in autophagy–lysosome-mediated clearance [97]. This finding suggests that mitochondrial quality control in RPE cells may fail when the initiation of mitophagy is not matched by effective autolysosomal clearance; this state may be further aggravated by impaired mitochondrial biogenesis in *PGC-1α/NFE2L2*-deficient settings. Beyond the canonical PINK1/Parkin pathway, the transient receptor potential mucolipin 1 (TRPML1)–transcription factor EB (TFEB) axis may provide an important auxiliary mechanism for mitochondrial quality control. TRPML1 activation promotes TFEB-dependent lysosomal biogenesis and mitophagy, thereby alleviating mitochondrial injury and improving redox homeostasis [98]. Moreover, beyond its role in LC3 recruitment, optineurin (OPTN) can promote phagosome maturation, facilitate phagosome–lysosome fusion, and enhance lysosome biogenesis by activating TRPML1-dependent TFEB, thereby helping RPE cells cope with the phagocytic burden imposed by outer segments [99]. These observations indicate that mitochondrial quality control in outer-retinal cells is closely linked to lysosomal function. Together, these findings indicate that mitochondrial quality control represents an important regulatory mechanism through which PRs and RPE cells respond to mitochondrial injury. When this quality-control network is inadequate, damaged mitochondria may persist abnormally, increasing outer-retinal susceptibility to oxidative stress and, plausibly, to ferroptosis-associated lipid peroxidation.

4.3. Insufficient Mitochondrial Biogenesis Capacity

In addition to mitochondrial dynamics and quality control, PRs must continuously replenish their mitochondrial pool to maintain mitochondrial homeostasis. PGC-1α is a canonical transcriptional coactivator of mitochondrial biogenesis that regulates the expression of nuclear-encoded mitochondrial proteins and transcriptional programs involved in oxidative metabolism and mitochondrial renewal [100]. In rd1 mice, the PGC-1α activator ZLN005 enhanced mitochondrial biogenesis, improved visual function, and delayed PR degeneration [101]. Evidence from a P23H retinitis pigmentosa model similarly showed that pharmacological upregulation of PGC-1α and mitochondrial transcription factor A (TFAM) was associated with activation of mitochondrial biogenesis and preservation of visual function, supporting the broader relevance of mitochondrial biogenesis in inherited PR degeneration [102].

At the level of mitochondrial gene expression, nuclear respiratory factor 1 (NRF1) and TFAM cooperate to support mitochondrial biogenesis and maintain mitochondrial DNA (mtDNA) expression. In a rod-specific *Nrf1*-knockout model, inner-segment mitochondria displayed abnormal morphology, aberrant subcellular positioning, and impaired function; these changes were accompanied by loss of TFAM expression and reduced cytochrome c oxidase (COX) activity and ultimately led to progressive rod degeneration and secondary cone loss [103]. These findings indicate that sustained mitochondrial renewal is essential for preserving mitochondrial function and PR survival.

In addition, impaired mitochondrial biogenesis in the RPE may further destabilize outer-retinal homeostasis. Inhibition of PGC-1α disrupts lipid metabolism and promotes lipid droplet accumulation in RPE cells [104]. In ARPE-19 cells, copper exposure increased peroxisome proliferator-activated receptor gamma coactivator 1-beta (PGC-1β) and TFAM expression, enhanced cytochrome c oxidase activity, and increased mitochondrial mass and mtDNA copy number, indicating that RPE respiratory-chain function is closely linked to mitochondrial biogenesis programs [105]. Because the RPE and PRs remain tightly coupled metabolically, insufficient mitochondrial

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renewal in the RPE may indirectly increase PR vulnerability to oxidative and metabolic stress by weakening RPE metabolic support and redox buffering capacity.

4.4. Mitochondrial Iron Burden and Disruption of Membrane Homeostasis

Mitochondria serve as key sites for iron–sulfur (Fe–S) cluster biogenesis and cellular iron regulation. Consequently, disturbances of iron import, utilization, or export can disrupt mitochondrial iron homeostasis and exacerbate oxidative stress [106,107]. With respect to mitochondrial iron import, evidence from KU812 and K562 leukemia-cell models has identified the poly(rC)-binding protein 2 (PCBP2)–translocase of outer mitochondrial membrane 20 (TOM20)–sideroflexin 3 (SFXN3) axis as a potential route for cytosolic iron entry into mitochondria. Functionally, knockdown of PCBP2 or SFXN3 in these leukemia-cell systems reduces catalytic ferrous iron within mitochondria and mitochondrial respiratory capacity, whereas SFXN3 overexpression causes mitochondrial Fe(II) accumulation and increases sensitivity to RAS-selective lethal 3 (RSL3)-induced ferroptosis [108].

In the retina, Sfxn3 mutations cause progressive outer retinal degeneration, including RPE thinning, suggesting that SFXN3 is required for outer-retinal homeostasis; whether this phenotype reflects altered mitochondrial iron handling or ferroptosis remains unresolved [109]. Mitochondrial membrane homeostasis may likewise influence PR susceptibility to iron-dependent lipid peroxidation. In the inner mitochondrial membrane, cardiolipin (CL) is a signature phospholipid that supports the organization and stability of respiratory-chain supercomplexes [110]. In CL-lacking yeast respiratory-supercomplex and PCBP1-depleted mouse-liver models, depletion of cardiolipin and coenzyme Q (CoQ) is associated with impaired respiratory-chain function, reduced oxygen consumption, and insufficient ATP production [111]. These findings suggest that disruption of inner mitochondrial membrane lipid homeostasis may promote oxidative injury by impairing respiratory-chain function and weakening mitochondrial bioenergetic stability.

At the outer mitochondrial membrane, abnormal protein homeostasis and increased membrane permeability may further drive cells toward irreversible injury. In dibutyl phthalate-exposed zebrafish ZF4 cells, upregulation and oligomerization of voltage-dependent anion channel 2 (VDAC2) are accompanied by mitochondrial iron overload and loss of mitochondrial membrane potential, contributing to ferroptosis [112]. In BALB/c mice and neonatal rat cardiomyocytes exposed to trastuzumab-related cardiotoxic stress, the lipid peroxidation product 4-hydroxynonenal (4-HNE) can bind to VDAC1 and promote its oligomerization, leading to the opening of the mitochondrial permeability transition pore (mPTP), dissipation of membrane potential, and ATP depletion [113]. Consistently, in DU145 and 22Rv1 prostate cancer cells, VDAC1 oligomers can form aberrant channels in the outer mitochondrial membrane, increasing mitochondrial ROS (mtROS), depleting GSH, dissipating membrane potential, and enhancing susceptibility to ferroptosis [114].

Although these VDAC-related findings come mainly from zebrafish ZF4 cells, trastuzumab-treated cardiomyopathy models, and DU145/22Rv1 prostate cancer cells rather than PRs, they suggest that mitochondrial outer-membrane channel remodeling can couple mitochondrial permeability changes to redox imbalance and regulated cell death. In retinal models, inhibition of VDAC1 oligomerization likewise alleviates mitochondrial dysfunction and attenuates PANoptosis-associated injury [115]. However, whether VDAC oligomerization directly contributes to PR ferroptosis remains unproven. A schematic synthesis of these mitochondrial homeostatic mechanisms is provided in Figure 3, and the evidence supporting each mitochondrial homeostatic axis is summarized in Table 1.

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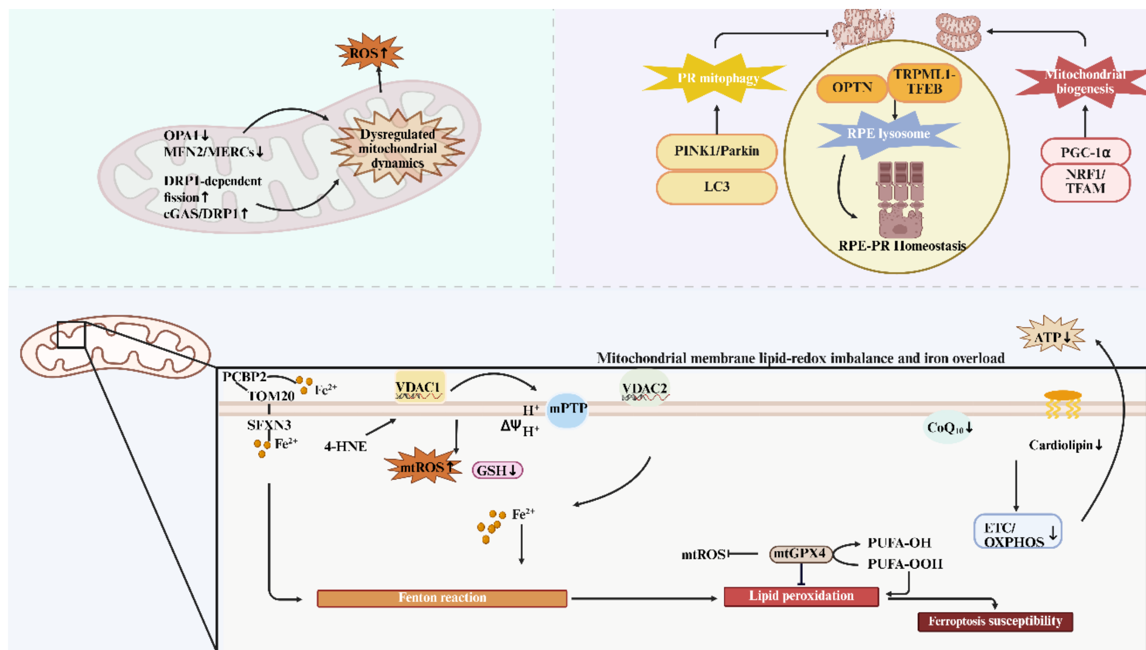

Figure 3. Mitochondrial homeostatic mechanisms that modulate photoreceptor susceptibility to ferroptosis-associated injury.

Table 1. Evidence-graded mitochondrial homeostatic axes regulating photoreceptor susceptibility to ferroptosis-associated injury.

Mechanistic axis	Key mechanism	Main supporting model	Evidence level	Ref.
mtGPX4-dependent phospholipid detoxification	mtGPX4 detoxifies phospholipid hydroperoxides. PR-specific *Gpx4* loss causes rapid degeneration with outer-segment, ciliary, and mitochondrial defects; mtGPX4 loss increases peroxidized DHA-containing PE and promotes cone–rod loss.	PR-specific *Gpx4* knockout mice; mtGPX4 knockout mice	A	[37,38]
OPA1/mitofusin-dependent fusion and PR mitochondrial architecture	Mitochondrial fusion maintains rod PR morphology and metabolism. OPA1 loss disrupts inner-segment mitochondrial alignment and inner-membrane organization.	Rod PR mitofusin models; PR OPA1 models; OPA1 structural studies	B	[45,79,80]
MFN2–MERC/IP3R Ca^{2+} coupling	MFN2 maintains MERC structure; disruption of MERC/IP3R-mediated Ca^{2+} handling may alter mitochondrial ROS/lipid homeostasis and contribute to hypoxic PR injury; SH-SY5Y neuroblastoma-cell ferroptosis data support IP3R-mediated mitochondrial Ca^{2+} overload.	MFN2/MERC models; hypoxic PR injury; SH-SY5Y neuroblastoma-cell ferroptosis model	B	[81–84]
DRP1-dependent mitochondrial fission	DRP1 activation and mitochondrial fragmentation accompany ferroptosis in NIH-3T3/HT-1080/H441/A549 cells, *Drp1*fl/fl MEFs, and HT22 neurons; diabetic retinas and high-glucose-treated 661W cells show p-DRP1,	NIH-3T3/HT-1080/H441/A549 cells, *Drp1*fl/fl MEFs, and HT22 neurons; T1DM-NDR retina; high-glucose 661W	B	[85–89]

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Mechanistic axis	Key mechanism	Main supporting model	Evidence level	Ref.
	fragmentation, cristae disruption, and membrane-potential loss.	cells; AMD donor RPE		
cGAS–STING inflammatory amplification	Mitochondrial and DNA damage can activate cGAS–STING; retinal oxidative stress and PR degeneration show pathway activation, whereas the cGAS–DRP1–ferroptosis link remains largely based on non-retinal cancer-cell models.	Cancer-cell models with mitochondria-localized cGAS; degenerating retina and microglial activation models	B	[90–92]
PINK1/Parkin and TRPML1–TFEB/OPTN quality control	Mitophagy and lysosomal biogenesis remove damaged mitochondria. Evidence from the developing retina, H_2O_2-treated 661W cells, and RPE models supports this quality-control axis.	Developing retina; H_2O_2-treated 661W cells; *PGC-1α/NFE2L2*-deficient and phagocytic RPE models	B	[93–99]
PGC-1α/NRF1/TFAM mitochondrial biogenesis	Mitochondrial biogenesis supports PR energy metabolism. PGC-1α activation protects rd1/P23H models; rod *Nrf1* loss causes mitochondrial dysfunction and PR degeneration; RPE biogenesis defects may weaken PR support.	rd1 and P23H RP models; rod-specific *Nrf1* models; RPE biogenesis/metabolism studies	B	[100–105]
PCBP2–TOM20–SFXN3 mitochondrial iron entry	KU812/K562 leukemia-cell data identify this axis as a mitochondrial iron-entry route and RSL3-sensitivity modifier. *Sfxn3* mutations cause progressive outer-retinal degeneration in mice.	KU812/K562 leukemia-cell mitochondrial iron-entry models; *Sfxn3* mutant retina	C	[106–109]
Cardiolipin/CoQ inner-membrane lipid homeostasis	Cardiolipin and CoQ support respiratory-chain supercomplex organization, respiration, and ATP production; cardiolipin-lacking yeast and PCBP1-depleted mouse-liver models link CL/CoQ depletion to bioenergetic impairment.	Cardiolipin-lacking yeast respiratory-supercomplex model; PCBP1-depleted mouse-liver model	C	[110,111]
VDAC1/2 oligomerization and mitochondrial permeability	VDAC oligomerization can couple permeability changes to mtROS production, GSH depletion, membrane-potential loss, and ferroptosis in zebrafish ZF4, cardiomyocyte, and prostate-cancer-cell models; retinal VDAC1 evidence mainly relates to ischemia/PANoptosis.	Zebrafish ZF4 cells; trastuzumab-treated BALB/c mouse/neonatal rat cardiomyocyte models; DU145/22Rv1 prostate cancer cells; retinal ischemia–reperfusion injury	C	[112–115]

Note: Evidence level A indicates direct photoreceptor/retinal genetic or pharmacological evidence linking the axis to ferroptosis- or lipid-peroxidation-associated photoreceptor degeneration; B indicates photoreceptor/retinal or outer-retinal evidence for mitochondrial/homeostatic injury with an indirect ferroptosis link or partial support from non-retinal ferroptosis models; C indicates mechanisms supported mainly by non-retinal studies or indirect retinal observations and requiring further photoreceptor-specific validation.

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5. Imbalance in the RPE–PR Metabolic Ecosystem as a Trigger and Amplifier of PR Ferroptosis-Associated Injury

5.1. Impaired Outer Segment Phagocytosis: Disrupted Lipid Recycling and Iron Homeostasis

In aged mouse RPE, cell loss is accompanied by reduced phagosome-processing capacity, suggesting an age-related decline in post-phagocytic processing by the RPE [116]. Additional evidence for phagocytosis-related pathology comes from abnormalities in the Mer tyrosine kinase (MERTK) pathway. Pharmacological inhibition of MERTK leads to the accumulation of shed POS, increased phagosome and phagolysosome numbers within the RPE, delayed POS renewal, and early PR injury [117]. In models of MERTK deficiency, suppression of microglial activation delays retinal degeneration, suggesting that phagocytic failure is followed by secondary inflammatory injury [118]. Inadequate phagocytic processing also increases the burden on the RPE to degrade oxidatively modified outer-segment-derived substrates.

Krohne et al. found that uptake of 4-HNE- or MDA-modified POS promoted the accumulation of lipofuscin-like autofluorescent granules in RPE cells; this process was accompanied by lysosomal dysfunction and reduced autophagic activity [119]. Escrevente et al. showed that lipofuscin-like granules in the RPE may arise from phagosomes containing incompletely digested POS and that insufficient lysosomal acidification or reduced hydrolytic activity further exacerbated granule accumulation [120]. These findings indicate that impaired lysosomal degradation after phagocytosis contributes importantly to the persistent retention of POS-derived by-products. In addition, lipofuscin accumulation within the RPE can promote lysosomal membrane permeabilization and induce atypical necroptosis-like injury, thereby further exacerbating intracellular stress in RPE cells [121]. Such lysosomal stress may compromise the ability of the RPE to maintain outer-retinal homeostasis.

Beyond inflammatory amplification, insufficient phagocytic processing may also perturb redox and iron homeostasis within the RPE–PR functional unit. In sodium iodate models, ferritin in the RPE is associated with autophagy- and lysosome-related markers, and ferritin-containing vesicles can be released into the extracellular space, suggesting that, under stress conditions, the RPE may influence the local iron burden of neighboring outer-retinal cells through vesicle-associated pathways [122]. Therefore, the pathological consequences of defective outer-segment phagocytosis extend beyond prolonged retention of uncleared POS. Defective phagocytic processing also impairs the ability of the RPE to degrade, transport, and recycle outer-segment-derived lipids, thereby weakening the metabolic buffering capacity required to accommodate the increased lipid burden within the RPE–PR functional unit.

5.2. Disrupted Glucose–Lactate Partitioning and Weakening of Antioxidant Defenses Against Lipid Peroxidation

Glucose transport and lactate shuttling between the RPE and PRs together constitute a critical component of metabolic coupling in the outer retina. When this transcellular substrate partitioning is disrupted, the consequences extend beyond energy-supply imbalance; they also include impaired central carbon metabolism, which is required to sustain reducing power and protect PRs against lipid peroxidation. Lactate transport across the RPE–PR interface depends heavily on monocarboxylate transporters such as MCT1 and MCT3, as well as on their chaperone protein BSG; in *Bsg*-deficient models, maturation and membrane localization of the relevant MCTs are impaired, and this impairment is accompanied by metabolic disorganization in the outer retina and abnormal electroretinographic (ERG) responses [61].

Models of RPE mitochondrial dysfunction further support this view. In the RPE, impaired mitochondrial electron transport can induce pseudohypoxia, enhance aerobic glycolysis, and promote dedifferentiation, ultimately leading to structural and functional abnormalities in PRs. Activation of an alternative oxidase (AOX)-mediated electron transport bypass can partially reverse

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these metabolic abnormalities and ameliorate the associated retinal phenotypes [123]. Together with metabolic-exchange studies showing glucose–lactate transfer between PRs and the RPE [51–53], these findings suggest that impaired RPE oxidative metabolism may weaken the substrate-partitioning pattern that normally helps preserve glucose availability for PRs. For PRs, the consequences of reduced glucose availability also extend beyond insufficient energy supply. PR-specific loss of glucose transporter 1 (GLUT1) leads to outer-segment shortening, reduced opsin levels in rods and cones, and ultimately impaired rod survival [55].

Consistent with this, simultaneous deletion of *HK2* and *PKM2* in rod photoreceptors causes early abnormalities in central glucose metabolism before overt cell loss becomes apparent. These abnormalities include reduced levels of the pentose phosphate pathway (PPP) intermediate sedoheptulose-7-phosphate (S7P) and are accompanied by thinning of the photoreceptor inner and outer segments, as well as thinning of the outer nuclear layer [59]. In addition, NADPH generated through the PPP contributes to GSH homeostasis in the retina [124]. Available evidence further indicates that GSH depletion markedly reduces the tolerance of PRs to lipid-peroxidation-associated injury [65]. Taken together, disruption of central carbon metabolism may indirectly weaken the antioxidant buffering capacity of PRs.

5.3. Impaired Retinaldehyde Clearance: atRAL and A2E-Driven Lipid Peroxidation and Ferroptosis-Associated Injury

Within PR outer-segment disc membranes, atRAL reversibly reacts with PE to form N-retinylidene-phosphatidylethanolamine (NRPE). When retinaldehyde handling or ATP-binding cassette subfamily A member 4 (*Abca4*)-dependent transport is impaired, bisretinoid precursors and related lipid abnormalities may accumulate in the outer retina and RPE, increasing the burden of by-products such as N-retinylidene-N-retinylethanolamine (A2E) and contributing to Stargardt-like lipid dyshomeostasis [125,126]. Chen et al. showed that, in models of defective atRAL clearance, atRAL overload was accompanied by elevated Fe^{2+} levels, acyl-CoA synthetase long-chain family member 4 (ACSL4) upregulation, and suppression of xCT–GSH-dependent antioxidant defense, resulting in ROS accumulation, exacerbation of lipid peroxidation, and PR loss [18].

Additional studies have shown that atRAL promotes Fe^{2+} release by upregulating heme oxygenase-1 (HO-1), thereby exacerbating ROS-dependent lipid peroxidation [127]. c-Jun N-terminal kinase (JNK)/c-Jun/nuclear receptor coactivator 4 (NCOA4) signaling can further expand the labile iron pool by enhancing ferritinophagy, thereby aggravating atRAL-induced ferroptosis-associated injury [128]. Taken together, these findings suggest that defective atRAL clearance may not only increase lipid-peroxidation stress in PRs but also amplify ferroptosis-associated injury by disrupting iron homeostasis. Beyond the direct toxicity of atRAL to PRs, dysregulated retinaldehyde handling may also promote oxidative stress in the RPE by driving bisretinoid accumulation. In A2E-loaded RPE cells, blue-light exposure increases Fe^{2+} levels, depletes GSH, and suppresses the SLC7A11–GPX4 pathway in the RPE, and these changes are accompanied by canonical ferroptosis-associated features [129].

Consistent with this, mice with RPE-specific *Gpx4* deletion exhibit loss of RPE polarity, accumulation of lipid-peroxidation products, complement activation, and secondary PR loss [130]. These findings suggest that redox imbalance within the RPE may further amplify injury in the outer retina. Overall, timely atRAL clearance is a critical mechanism by which PRs limit the accumulation of phototransduction-related retinoid by-products. When atRAL clearance fails, reactive retinoid intermediates are more likely to accumulate in both PRs and the RPE, thereby promoting oxidative stress and lipid-peroxidation-associated injury.

6. Therapeutic Strategies: Reducing the Biological Susceptibility of PRs to Ferroptosis-Associated Injury

6.1. Interrupting the Chain Reaction of Lipid Peroxidation

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Among current experimental therapeutic strategies, direct interruption of the lipid-peroxidation cascade is a major approach for limiting ferroptosis-associated injury in PRs. In both bright-light-induced retinal injury models and models with defective atRAL clearance, Fer-1 attenuated ferroptosis-associated changes and alleviated PR degeneration [18,131], supporting the protective potential of chain-breaking interventions. However, blocking radical propagation alone may not be sufficient to fully suppress the injury cascade. Targeting upstream drivers of lipid peroxidation is therefore also therapeutically valuable. Consistent with this view, reducing mtROS can lessen the upstream oxidative pressure that drives lipid peroxidation.

In both atRAL-treated 661W cells and light-exposed *Abca4*−/− retinol dehydrogenase 8 (*Rdh8*)−/− double-knockout mice, Mito-TEMPO suppressed mtROS accumulation and lipid peroxidation, alleviated abnormalities in iron homeostasis, and ameliorated retinal degeneration [132]. These findings suggest that limiting mitochondrial oxidative stress can partially attenuate ferroptosis-associated injury in atRAL-related models. Likewise, restricting iron-catalyzed oxidative reactions can blunt the upstream amplification of lipid peroxidation. In light-induced retinal injury models, deferiprone reduced photoreceptor death and attenuated oxidative-stress-related changes, including altered heme oxygenase 1 (Hmox1), ceruloplasmin (Cp), and complement component 3 (C3) expression, as well as nitrotyrosine levels [133].

In rd10 mice, the zinc (Zn)–desferrioxamine (DFO) complex exerted stronger protective effects than Zn or DFO alone by improving electroretinographic responses, attenuating structural degeneration of PRs, and reducing oxidative-damage markers and ferritin-associated iron [134]. Taken together, these findings indicate that suppressing mitochondrial ROS and iron-driven oxidative stress can weaken the lipid-peroxidation cascade. Enhancing endogenous peroxide detoxification capacity is another key strategy. As discussed above, loss of mitochondrial GPX4 (mtGPX4) results in the accumulation of peroxidized DHA-containing PE species in the retina and progressive PR loss [38]. Maintenance of GPX4-dependent detoxification is therefore essential for PR homeostasis.

Consistent with this, inducible upregulation of GPX4 protected retinal structure and function in multiple oxidative injury models [135], whereas SLC7A11 overexpression suppressed light-induced ferroptosis-associated pathways and photoreceptor degeneration [15]. Strengthening peroxide detoxification via the xCT–GSH–GPX4 axis may thus represent an additional therapeutic approach to suppress lipid-peroxidation-associated injury. At the substrate level, reducing the oxidative susceptibility of PUFA-rich membrane lipids may further lower PR susceptibility to ferroptosis. Liu et al. showed that deuterated DHA suppressed the formation of the oxidative product carboxyethylpyrrole (CEP) in a model of retinal iron overload and markedly preserved outer-retinal structure and function [136]. This finding suggests that reducing the intrinsic reactivity of PUFA-rich membrane lipid substrates can limit the initiation and amplification of lipid-peroxidation chain reactions at the substrate level.

Several natural products have shown experimental therapeutic potential by simultaneously modulating iron homeostasis, redox status, and mitochondrial function. Evidence from oxidative-injury models, including H_2O_2-treated 661W cells and rd10 mice, shows that Fructus Lycii and Salvia miltiorrhiza extract (FSE) alleviates ferroptosis-associated injury in PRs and modulates the p53–SLC7A11–GPX4 signaling axis; Fer-1 produced similar antiferroptotic effects in these models [137]. Similarly, in 661W cells with atRAL accumulation, crocin attenuated oxidative stress, mitochondrial damage, Fe^{2+} accumulation, and lipid peroxidation, while also modulating the Kelch-like ECH-associated protein 1 (KEAP1)–NRF2–HO-1 pathway. Salvianic acid A (SAA), in turn, reduced iron deposition, lipid peroxidation, and mitochondrial damage in iron-overload models and modulated the expression of ferroptosis-related molecules, including ACSL4, GPX4, and SLC7A11 [20,138].

Overall, ferroptosis-associated PR injury may be mitigated not only by directly interrupting the lipid-peroxidation cascade but also by suppressing mitochondrial ROS and iron-driven oxidative stress, enhancing peroxide detoxification through the xCT–GSH–GPX4 axis, and reducing the

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intrinsic reactivity of oxidation-prone membrane lipid substrates. Together, these approaches may reduce PR vulnerability to lipid-peroxidation-associated injury.

6.2. Stabilizing Mitochondrial Redox Homeostasis, Dynamics, and Quality Control

Promoting the clearance of damaged mitochondria and limiting pathological fission may reduce PR susceptibility to ferroptosis-associated injury by preserving mitochondrial redox homeostasis. Among upstream regulators, AMP-activated protein kinase (AMPK) is a central kinase that links energy metabolism to mitochondrial homeostasis and coordinates mitochondrial biogenesis, dynamics, and mitophagy [139]. In models of acute light-induced injury and inherited retinal degeneration, metformin-mediated AMPK activation alleviated injury to PRs and the RPE, with concomitant reductions in oxidative stress and improvements in mitochondrial energy metabolism [140]. In high-glucose-treated 661W cells, AMPK activation improved mitochondrial membrane potential and morphology, increased mitochondrial DNA copy number, and upregulated PGC-1α–NRF1–TFAM signaling, and this was accompanied by increased LC3-II levels and reduced sequestosome 1 (p62/SQSTM1) levels [141].

Consistent with this, after bright-light-induced injury, the AMPK agonist 5-aminoimidazole-4-carboxamide ribonucleotide (AICAR) preserved retinal oxygen consumption, cytochrome c oxidase activity, and ATP levels while maintaining visual function and PR survival [142]. Beyond AMPK signaling, enhancing nicotinamide adenine dinucleotide (NAD^+) metabolism provides an additional strategy for mitochondrial protection. Nicotinamide riboside (NR) produced sustained increases in retinal NAD^+ levels, improved outer-retinal structure and function, and reduced apoptosis and inflammatory responses [143]. Nicotinamide mononucleotide (NMN), in turn, reduced infiltration by CD11b-positive inflammatory cells and PR death, decreased oxidative damage, preserved outer nuclear layer (ONL) thickness, and activated sirtuin 1 (SIRT1)–HO-1 signaling [144].

Taken together, these findings suggest that AMPK activation and NAD^+ metabolic support help preserve mitochondrial respiration, ATP supply, and stress-response capacity, thereby indirectly enhancing PR tolerance to oxidative stress and potentially reducing susceptibility to lipid-peroxidation-associated injury. From the standpoint of mitochondrial renewal and quality control, promoting mitochondrial biogenesis and enhancing the clearance of damaged mitochondria are also therapeutically relevant. The PGC-1α activator ZLN005 enhanced mitochondrial biogenesis, improved visual function, and preserved ONL thickness in rd1 mice [101]. In 661W cell models of oxidative injury, enhancement of PINK1/Parkin-mediated mitophagy and activation of the mitochondrial unfolded protein response (mtUPR) preserved mitochondrial membrane potential, supported mitochondrial quality control, and attenuated cellular injury [96]. In retinal detachment models, the TRPML1 agonist ML-SA1 also improved ONL structure and reduced PR apoptosis [145].

These findings indicate that strengthening mitochondrial renewal, mitophagy, and autophagy–lysosome-mediated clearance helps preserve mitochondrial quality-control capacity in PRs and may reduce their susceptibility to oxidative and lipid-peroxidation-associated injury. Stabilizing mitochondrial dynamics represents another feasible strategy. Multiple models support the view that pharmacological or genetic interventions can limit pathological fission in PR mitochondria. The DRP1 inhibitor Mdivi-1 ameliorated mitochondrial abnormalities in diabetic retinas and alleviated associated structural and functional damage [88]. Downregulation of *microRNA-181a* (*miR-181a*) and *microRNA-181b* (*miR-181b*) modulated Drp1 expression, reduced excessive mitochondrial fragmentation in rhodopsin P347S (RHO-P347S) photoreceptors, and delayed the progression of inherited retinal degeneration [146].

In retinal detachment models, She et al. further showed that injury activated a ROS–DRP1-dependent mitochondrial fission pathway in PRs, whereas DRP1 inhibition preserved mitochondrial structure and alleviated PR damage [147]. Overall, improving mitochondrial energy metabolism, enhancing mitochondrial renewal and quality control, and limiting pathological fission may collectively represent promising strategies for reducing PR susceptibility to oxidative stress and ferroptosis-associated lipid peroxidation. These interventions share a common feature: they enhance

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the tolerance of PRs to oxidative stress, membrane lipid peroxidation, and mitochondrial injury by stabilizing mitochondrial homeostasis.

6.3. Restoring RPE–PR Metabolic Coupling and Iron Homeostasis

Post-phagocytic processing of POS, monocarboxylate transport, and the visual cycle collectively sustain metabolic coupling between the RPE and PRs in the outer retina [33,50,60,148]. When this coupling is disrupted, PRs may experience abnormal substrate supply and increased oxidative stress. Accordingly, restoring post-phagocytic processing, oxidative metabolism, and local iron buffering in the RPE may provide an upstream strategy for reducing PR susceptibility to ferroptosis-associated injury. Restoration of post-phagocytic POS processing and phagosome maturation in the RPE may help re-establish lipid turnover and substrate allocation in the outer retina. One study showed that human fetal retinal pigment epithelium (hfRPE) and ARPE-19 cells exhibited increased β-hydroxybutyrate (β-HB) release following POS phagocytosis, whereas RPE explants from melanoregulin-deficient (*Mreg*−/−) and *Abca4*−/− mice displayed delayed peak β-HB release relative to peak phagocytic activity [47].

Consistent with this, aged mouse RPE displays reduced post-phagocytic processing capacity [116], whereas pharmacological suppression of mitochondrial fission improves POS phagocytosis in RPE models of aging-related mitochondrial dysfunction [149]. In Royal College of Surgeons (RCS) rats, RPE-targeted delivery of AAV8-Y733F-bestrophin 1 (BEST1)-human MERTK (hMERTK) conferred long-term retinal protection, further supporting the view that restoration of RPE phagocytic function helps maintain outer-retinal homeostasis [150]. Taken together, these findings indicate that improving post-phagocytic processing in the RPE may reduce the retention of POS-derived lipids and their oxidatively modified products in the outer retina, thereby reducing oxidative pressure in the microenvironment surrounding PRs. In addition, restoring oxidative metabolism and strengthening antioxidant defenses against lipid peroxidation in the RPE may provide another means of supporting PR metabolism.

In models of RPE electron transport chain (ETC) deficiency, RPE-specific expression of AOX partially reversed pseudohypoxia-associated metabolic reprogramming and differentiation defects, improved cellular stress responses, and preserved retinal structure and function [123]. Consistent with this, in models with RPE-specific *Gpx4* deletion, lipid peroxidation products such as acrolein, MDA, and 4-HNE accumulated in the RPE, and pharmacological suppression of lipid peroxidation-related injury, such as Fer-1 or α-tocopherol treatment, alleviated RPE degeneration and secondary PR loss [130]. Strengthening defenses against lipid peroxidation in the RPE may therefore protect the RPE itself while indirectly reducing PR exposure to oxidative stress and the risk of ferroptosis-associated injury. Beyond restoring metabolic support, enhancing iron buffering and iron transport in the RPE may also help prevent local iron dyshomeostasis from affecting PRs.

Intraocular iron injection induces PR death and oxidative injury in the outer retina and subsequently elicits geographic atrophy (GA)-like changes [151], underscoring the sensitivity of the outer retina to disturbed iron homeostasis. Consistent with this, aqueous humor samples from patients with early GA show elevated iron levels and reduced transferrin iron-binding capacity. In induced pluripotent stem cell (iPSC)-derived RPE models, transferrin (TF) supplementation improved iron homeostasis and attenuated oxidative stress, mitochondrial injury, and ferroptosis-associated changes [152]. Moreover, TF-based non-viral gene therapy further supports iron buffering as a retinal-protective strategy, because sustained intraocular TF production delayed structural and functional degeneration in the RCS rat model of retinitis pigmentosa and reduced ocular malondialdehyde levels [153]. Taken together, these findings suggest that therapeutic strategies directed at the RPE–PR unit—particularly restoration of POS-processing capacity, RPE oxidative metabolism, and local iron-buffering capacity—may help reduce the pro-oxidative microenvironment surrounding PRs and thereby lower their vulnerability to ferroptosis-associated injury [154,155]. These therapeutic strategies are summarized in Table 2.

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Table 2. Therapeutic strategies for reducing photoreceptor susceptibility to ferroptosis-associated injury.

Strategy	Targeted vulnerability	Intervention nodes	Expected PR/RPE effect	Ref.
Interrupt lipid-peroxidation propagation	DHA/PUFA-rich outer-segment membranes; labile Fe^{2+}; mtROS-driven initiation; impaired xCT–GSH–GPX4 detoxification; oxidation-prone lipid substrates.	Fer-1/α-tocopherol; Mito-TEMPO; deferiprone/Zn–DFO; SLC7A11/GPX4 support; deuterated DHA; FSE, crocin, and SAA as multitarget redox/iron modulators.	Limits lipid-radical propagation, Fe^{2+}/mtROS-driven amplification, and PUFA oxidizability; enhances phospholipid-hydroperoxide detoxification.	[15,18,20,38,130–138]
Restore PR mitochondrial redox homeostasis and quality control	High PR energy demand; mtROS leakage; impaired ATP production; defective biogenesis/mitophagy; insufficient autophagy–lysosome clearance; excessive DRP1-dependent fission.	AMPK activation with metformin/AICAR; NAD^+ support with NR/NMN; PGC-1α–NRF1–TFAM activation with ZLN005; PINK1/Parkin and mtUPR activation; TRPML1–lysosomal support; DRP1 inhibition or *miR-181a/b* downregulation.	Preserves respiration, membrane potential, ATP supply, and antioxidant buffering; promotes mitochondrial renewal and clearance; reduces fission-associated mtROS and lipid-peroxidation pressure.	[88,96,101,139–147]
Restore RPE–PR metabolic support and local iron buffering	RPE post-phagocytic POS-processing failure; oxidized POS/lipofuscin burden; abnormal glucose–lactate or ketone support; RPE oxidative/ferroptotic stress; reduced local iron buffering.	MERTK-directed restoration of POS phagocytosis/phagosome maturation; post-phagocytic processing support; modulation of RPE mitochondrial dynamics; AOX rescue of RPE ETC dysfunction; RPE lipid-peroxidation defense with Fer-1/α-tocopherol in RPE-specific *Gpx4* models; transferrin supplementation/overexpression.	Improves lipid recycling and substrate allocation; limits oxidized POS-derived lipids; strengthens RPE antioxidant support; buffers labile iron and reduces secondary oxidative pressure on PRs.	[47,116,123,130,148–153]

7. Conclusions and Perspectives

This review frames PR vulnerability to ferroptosis-associated injury as a multilayered biological state shaped by the properties of membrane lipid substrates, mitochondrial homeostasis, and the RPE–PR microenvironment. From this perspective, we have discussed the DHA-enriched lipid composition of PR outer segments, the chronically high metabolic demand and spatially specialized mitochondrial organization of PRs, and the RPE–PR metabolic coupling sustained by outer-segment renewal, phagocytic turnover, glucose transport, lactate shuttling, and the visual cycle. We have also summarized defense systems against lipid peroxidation, focusing on the xCT–GSH–GPX4 axis and mtGPX4. Disturbances in mitochondrial dynamics, quality control, and biogenesis, together with iron dyshomeostasis and disruption of the RPE–PR unit, may compromise both PR-intrinsic homeostasis and tissue-level metabolic support. Within this framework, impaired atRAL clearance and A2E/bisretinoid accumulation provide an important link between visual-cycle stress, iron dyshomeostasis, and lipid peroxidation, further supporting the integration of retinoid metabolism into the RPE–PR coupling framework. Accordingly, ferroptosis-associated injury in PRs should be regarded not simply as an isolated cell-death event but as a state of outer-retinal metabolic and redox decompensation driven by oxidation-prone membrane lipid substrates, mitochondrial homeostatic imbalance, and impaired metabolic support in the outer retina.

From a translational perspective, future interventions may need to extend beyond downstream scavenging of lipid radicals and instead be developed as combination strategies that reduce PR

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susceptibility to ferroptosis-associated injury. With respect to lipid-peroxidation stress, this may involve limiting iron-catalyzed oxidative reactions, strengthening peroxide detoxification through the xCT–GSH–GPX4 axis and mtGPX4-dependent defenses, and reducing the reactivity of PUFA-rich membrane lipid substrates. At the same time, greater emphasis should be placed on stabilizing mitochondrial dynamics, enhancing mitochondrial quality control, restoring mitochondrial turnover and energy metabolism, and re-establishing post-phagocytic processing, local iron buffering, and metabolic support in the RPE. Such strategies may reduce PR vulnerability to ferroptosis-associated injury early in the pathogenic cascade. Several key questions, however, remain unresolved, including stage-specific changes across different cell types during ferroptosis-associated injury in PRs and the optimal timing and combinations of interventions targeting the RPE, PRs, or both. Future studies should therefore pursue more cell-type-specific and combinatorial strategies that preserve, to the greatest extent possible, the membrane lipid composition and metabolic features required for visual function. Overall, the framework proposed here provides a conceptual basis for developing photoreceptor-protective strategies for blinding retinal diseases, including diabetic retinopathy, age-related macular degeneration, and inherited retinal degenerative disorders.

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Abbreviations

The following abbreviations are used in this manuscript:

4-HNE	4-hydroxynonenal
A2E	N-retinylidene-N-retinylethanolamine
AMD	age-related macular degeneration
AMPK	AMP-activated protein kinase
AOX	alternative oxidase
atRAL	all-trans-retinal
BH_4	tetrahydrobiopterin
CL	cardiolipin
CoQ_{10}	coenzyme Q_{10}
DHA	docosahexaenoic acid
DHODH	dihydroorotate dehydrogenase
DR	diabetic retinopathy
DRP1/*Drp1*	dynamin-related protein 1
ETC	electron transport chain
Fer-1	ferrostatin-1
FSP1	ferroptosis suppressor protein 1
GA	geographic atrophy
GCH1	GTP cyclohydrolase 1
GPX4/*Gpx4*	glutathione peroxidase 4

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GSH	glutathione
HO-1	heme oxygenase-1
LC- and VLC-PUFAs	long-chain and very-long-chain polyunsaturated fatty acids
LC3/LC3B	microtubule-associated protein 1 light chain 3/light chain 3 beta
MCT1/MCT3/MCTs	monocarboxylate transporter 1/3/(s)
MDA	malondialdehyde
MERC/MERCs	mitochondria–endoplasmic reticulum contact site(s)
MFN2	mitofusin 2
mtGPX4	mitochondrial glutathione peroxidase 4
mtROS	mitochondrial reactive oxygen species
mtUPR	mitochondrial unfolded protein response
NCOA4	nuclear receptor coactivator 4
NFE2L2/NRF2	nuclear factor erythroid 2-related factor 2 gene/protein
NRF1/*Nrf1*	nuclear respiratory factor 1
ONL	outer nuclear layer
OPA1	optic atrophy 1
OPTN	optineurin
PCBP2	poly(rC)-binding protein 2
PE	phosphatidylethanolamine
PGC-1α	peroxisome proliferator-activated receptor gamma coactivator 1-alpha
PINK1	PTEN-induced kinase 1
POS	photoreceptor outer segment(s)
PR	photoreceptor
PUFA/PUFAs	polyunsaturated fatty acid(s)
ROS	reactive oxygen species
RP	retinitis pigmentosa
RPE	retinal pigment epithelium
RPE65	retinal pigment epithelium-specific 65-kDa protein
RPE–PR	retinal pigment epithelium–photoreceptor
RSL3	RAS-selective lethal 3
SLC7A11	solute carrier family 7 member 11
TFAM	mitochondrial transcription factor A
TOM20	translocase of outer mitochondrial membrane 20
VDAC1/VDAC2	voltage-dependent anion channel 1/2
VEGF	vascular endothelial growth factor
xCT	cystine/glutamate antiporter

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