Review

The Metabolic Underpinnings of Retinal Health and Disease: A Focus on Photoreceptor Cells

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Abstract: The photoreceptor cells of the retina, encompassing rods and cones, are pivotal in the transduction of light signals into chemical ones, thereby initiating the visual process. This review explores the metabolic bedrock of these cells, which are not only crucial for preserving retinal health but are also susceptible to metabolic stress, precipitating a spectrum of retinal pathologies. The manuscript elucidates the intricate metabolic processes of photoreceptor cells, the synergistic metabolic interplay between photoreceptors and the retinal pigment epithelium (RPE), and appraises the metabolic shifts within photoreceptor cells under conditions of photic injury and diverse pathological states, as well as the ramifications of these metabolic perturbations for retinal function. The review culminates with a prospective horizon scan of research in photoreceptor cell metabolism, charting anticipated investigative trajectories.

Keywords: photoreceptor cells; retinal metabolism; retinal diseases

1. Introduction

The retina, often metaphorically described as the ‘window to the brain’, is a delicate and translucent tissue that adheres to the innermost layer of the choroid. It plays a cardinal role in the sensation of light. The retina’s photoreceptor cells, or visual cells, which include rods and cones, are instrumental in the initial phase of light sensation. These cells are unique within the retina for their ability to perceive light stimuli; other retinal cells react only indirectly to light, through the electrical or chemical signals emitted by photoreceptor cells upon stimulation. Consequently, damage to the photoreceptor layer can result in the absence of visual signals, rendering the visual system ineffective, even when other cells function optimally.

As the first stop in the visual pathway, the primary function of photoreceptor cells is to carry out the conversion of light signals into chemical signals. They are responsible for receiving light signals and transforming them into chemical signals to be passed on to downstream cells. The operation of photoreceptor cells begins with the reception of light signals and ends with the release of glutamate neurotransmitters to downstream cells. Through a series of biochemical reactions, they convert light stimuli into changes in membrane potential, then transform these changes into variations in the release of glutamate at the synaptic terminals, ultimately conveying the intensity of light signals to downstream bipolar cells in the form of glutamate release as a chemical signal. Normal retinal photoreceptor cells have a high demand for energy, making them susceptible to metabolic stress, and many diseases are closely related to their metabolism. This article summarizes the research progress on the metabolism of retinal photoreceptor cells, as well as the impact of related diseases on their metabolism, with the aim of providing reference suggestions for research related to the metabolism of retinal photoreceptor cells.

2. Structural Features and Distribution Characteristics of Retinal Photoreceptor Cells

Photoreceptor cells in the retina consist of four parts: the outer segment, inner segment, cell body, and synaptic terminal. The spatial organization of these components within the photoreceptor is illustrated in Figure 1. The cell body contains the nucleus and is responsible for integrating signals received from the outer segment and transmitting them to the bipolar cells in the retina. The synaptic terminal is equivalent to the axon, which connects

to bipolar cells via synapses, allowing for the transmission of signals to other neurons in the visual pathway. And the inner and outer segments are equivalent to the dendrites. The outer segment is the light-sensitive part of the photoreceptor cells, featuring a layered (or disc-shaped) structure formed by the infolding of the cell membrane that are rich in photopigments (such as rhodopsin in rods and indopsins in cones). The inner segment is slightly thicker and contains a large number of mitochondria, making it the most metabolically active part [1]. The outer and inner segments are connected, with nine pairs of small cilia extending from the inner segment into the outer segment, serving to transmit excitement and substances [2].

In the human retina, there are approximately 6 to 8 million cone cells and 120 million rod cells, distributed in different parts of the retina. Rod cells are primarily responsible for vision under low light conditions and are the main photoreceptor cells for night vision [3]. They are slender in shape and rich in rhodopsin, enabling them to perceive light in dim light [4]. Rod cells are mainly concentrated in the peripheral areas of the retina and are almost absent in the central fovea [5,6].

Cone cells are cells that sense strong light and color, and they are less sensitive to weak light and brightness than rod cells; however, they have a high resolution capacity for strong light and color [7]. The cell bodies of cone cells are shorter, with photoreceptive proteins, iodopsin, at their tips [8]. Cone cells are divided into three types based on different light wavelengths: short-wavelength (S-cones), medium-wavelength (M-cones), and long-wavelength (L-cones), corresponding to blue, green, and red light [9]. The long-wavelength (L-type) cones, which house the opsin OPN1LW, are responsible for detecting the red light region of the visible spectrum, approximately at 564 nm. The medium-wavelength (M-type) cones, expressing the opsin OPN1MW, capture the green light spectrum, around 534 nm. Lastly, the short-wavelength (S-type) cones, equipped with the opsin OPN1SW, are designed to perceive the blue light spectrum, at approximately 420 nm [10]. In the fovea of the macula in the retina, there are only cone cells, and light can directly reach these cells, making this area the most sensitive for light perception and color discrimination. In contrast, the peripheral part of the retina, which is mainly composed of rod cells, has lower light resolution, incomplete color vision, but is sensitive to dim light [11].

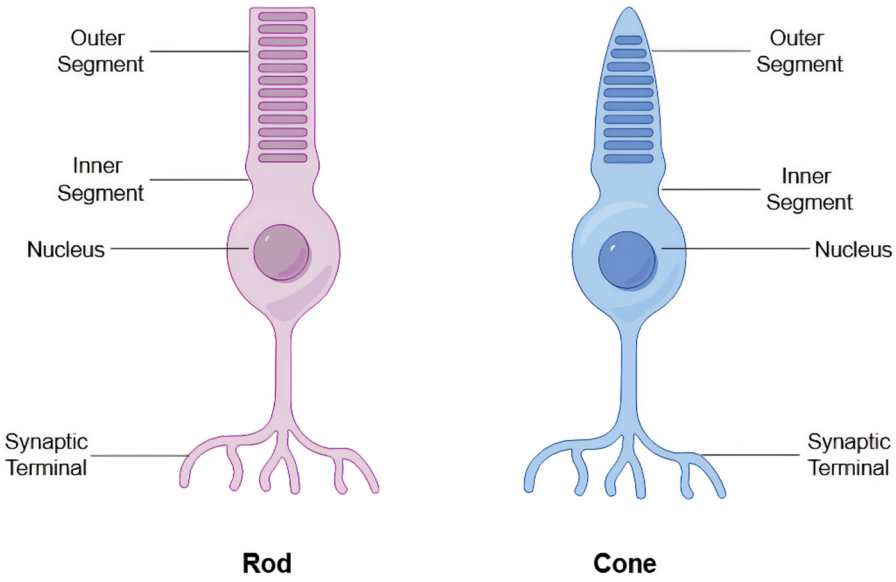

Figure 1. Photoreceptor structure.

3. Development and Differentiation of Retinal Photoreceptor Cells

In mammals, the maturation of photoreceptors is a protracted process, spanning several weeks to months post-final mitosis, with the duration varying among species [11–15]. The developmental trajectory of photoreceptors can be delineated into five pivotal stages: initially, the multiplication of pluripotent retinal progenitor cells (RPCs); subsequently, the constriction of the developmental horizons for RPCs; thereafter, the determination of cell fate and commitment to photoreceptor precursors, which may occur during or subsequent to the terminal mitotic division; next, the upregulation of genes that are integral to photoreceptors, encompassing those that participate in phototransduction and morphogenesis; and ultimately, the elongation of axons, the establishment of synaptic connections, and the genesis of outer segments [16].

During the initial phase of retinal development, multipotent retinal progenitor cells (RPCs) proliferate, generating more multipotent progenitors or precursors whose capacity to differentiate into various cell types is limited [17]. Certain of these proliferating cells are dedicated to a lineage that will produce at least one type of photoreceptor and potentially non-photoreceptive cells. Upon exiting the cell cycle, the post-mitotic precursors retain the potential for plasticity. Throughout the determination of photoreceptor cell types, these precursors are steered towards becoming either cone or rod cells, which will eventually express photopigments (indopsin in cones, rhodopsin in rods), and develop outer segments and synaptic connections [18–20].

4. The Warburg Effect in the Retina and the Metabolic Pathways of Photoreceptor Cells

The retina, a component of the central nervous system, exhibits the same elevated metabolic rate as the brain. Typically, the substantial energy requirements of the retina are met with an ample provision of metabolic substrates. Under normal conditions, the metabolic processes of retinal tissue and cells encompass both material metabolism and energy metabolism. Material metabolism primarily facilitates the continuous exchange of substances between the organism and its surrounding environment, with the main metabolic pathways being assimilation and dissimilation. Energy metabolism, on the other hand, involves a series of chemical reactions that sustain the vital activities of cells and tissues, which can be divided into anabolic and catabolic reactions.

4.1. The Warburg Effect in the Retina

The retina is one of the high-energy-consuming central nervous tissues in the human body, and the homeostasis of its energy metabolism plays an extremely important role in maintaining normal retinal function and repairing tissue function under pathological conditions [21]. Research has found that although glycolysis and oxidative phosphorylation are the main metabolic pathways for retinal energy metabolism, as part of the central nervous system, the retina's energy metabolism characteristics are similar to those of rapidly growing and metabolically demanding tumor tissues [22]. Even under oxygen-rich conditions, the retina primarily relies on glycolysis for energy supply, known as the Warburg effect in the retina [23,24]. In recent years, with the gradual deepening of research on the Warburg effect in the field of oncology, the Warburg effect in the retina and its mechanisms have gradually attracted attention. Studies have found that after animals were injected with iodoacetic acid, which inhibits glyceraldehyde-3-phosphate dehydrogenase and selectively suppresses the glycolytic pathway, their vision was severely impaired, indicating that the retina is sensitive to glycolysis reactions. Subsequent in vitro experiments also confirmed that about 80% of glucose in the retinal metabolic process is metabolized through the glycolytic pathway to produce a large amount of lactate [25,26]. In addition, research has found that retinal neural conduction activities are highly dependent on the activity of the glycolytic pathway, and when the glycolytic pathway is obstructed, the retinal light conduction activity is severely reduced [27].

4.2. The Metabolism of Retinal Photoreceptor Cells

The outermost layer of the retina consists of photoreceptor cells and the outer processes of Müller glial cells. Evidence suggests that glucose uptake and aerobic glycolysis predominantly occur in photoreceptors rather than in Müller glial cells. This is supported by two main findings. Firstly, in vivo studies have shown that glucose from the blood circulates through the retinal pigment epithelium (RPE) and reaches the photoreceptors. When the fluorescent glucose analog 2-NBDG is administered to mice, either through gavage [28], tail vein injection [29,30], or intraperitoneal injection [31], it becomes phosphorylated at the C6 position upon entering the cells, leading to its accumulation. Notably, the fluorescence intensity from 2-NBDG accumulation is significantly higher in photoreceptors compared to Müller cells [32], indicating a higher rate of glucose uptake in photoreceptors. And the second line of evidence comes from the observation that photoreceptors have a high concentration of glycolytic enzymes.

Photoreceptor cells in mammalian retinal tissue primarily rely on the glycolytic pathway for energy metabolism [32], with specific metabolic pathways illustrated in Figure 2. Furthermore, key enzymes that regulate the Warburg effect in cancer cells, such as hexokinase 2 (HK2) and pyruvate kinase M2 (PKM2), are highly expressed in retinal photoreceptor cells [33,34]. The degree of the Warburg effect in retinas from different species is positively correlated with the renewal ratio of rhodopsin in photoreceptor cells [35,36]. Additional research has found that photoreceptor cells in the retina produce a large amount of lactate and are sensitive to inhibitors of glycolytic pathway enzymes, regardless of whether they are in aerobic or anaerobic environments [27]. Specifically inhibiting glycolytic reactions reduces the synthesis of the outer segments of rod cells, leading to shorter outer segments [34], indicating that the level of glycolysis plays a significant role in the synthesis of rod cell outer segments.

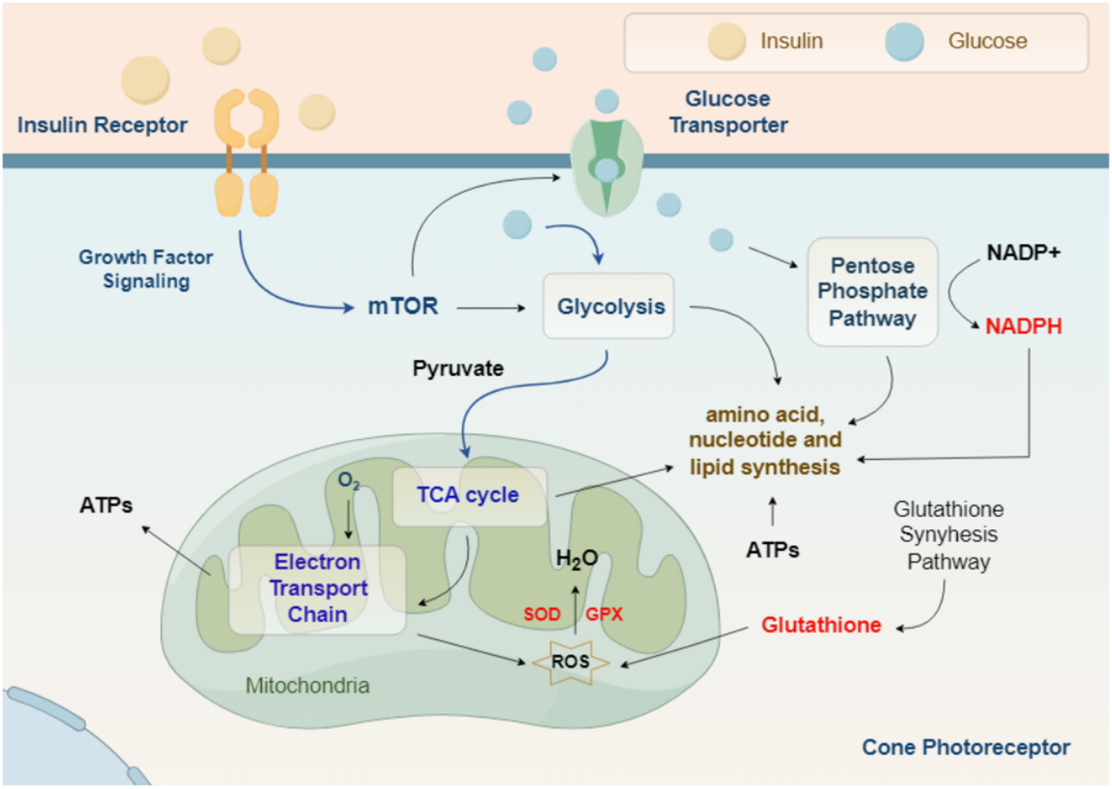

Figure 2. The metabolism of photoreceptor cells (using cone cells as an example).

4.3. The Significance of Glycolysis in the Metabolism of Retinal Photoreceptor Cells

The glycolytic pathway plays a crucial role in maintaining the physiological functions of retinal photoreceptor cells. Firstly, photoreceptor cells in vertebrate retinas exhibit high metabolic activity and consume considerable energy [37]. Compared to oxidative phosphorylation, the glycolytic pathway can produce ATP more rapidly to meet the energy demands of the cells. Secondly, glycolytic side pathways, such as the serine biosynthesis pathway and glycogen synthesis pathway, provide metabolic intermediates for amino acid synthesis. During the process of phototransduction, photoreceptor cells shed or renew a large number of membrane discs and synthesize rhodopsin, requiring substantial energy and amino acids to fulfill their synthetic metabolic needs [27]. Rhodopsin is a G-protein coupled receptor rich in serine. Intermediate metabolites of glycolysis, such as 3-phosphoglycerate, are converted into serine under the action of a series of enzymes, providing raw materials for the synthesis of phosphatidylserine and sphingosine, and the glycosylation process of rhodopsin requires polysaccharides mainly generated from the intermediate product 6-phosphofructose through glycolysis [38,39].

The intermediate metabolite 6-phosphogluconate of the glycolytic pathway can also produce nicotinamide adenine dinucleotide phosphate (NADPH) through the pentose phosphate pathway, which is significant for fatty acid biosynthesis, maintaining cellular redox status, inhibiting apoptosis, and reducing phototoxicity (promoting the conversion of retinal to all-trans retinol) [40]. Although the pentose phosphate pathway accounts for only 1.5% to 10% of glucose oxidative metabolism, it has been found in rat retinal cell cultures that blocking this pathway leads to increased rates of apoptosis and necrosis, indicating its extremely important role in the metabolism of retinal photoreceptor cells [41].

4.4. Metabolic Relationship between Retinal Photoreceptor Cells and RPE Cells

In general, we can consider the photoreceptor cells and RPE cells on the retina as a metabolic system, where they have distinct roles yet interact with each other to work in concert. The retina's photoreceptor and RPE cells function as a metabolic unit, each with specific roles that complement each other for synchronized operation.

When RPE cells are lost, photoreceptors also cease to function. Administering sodium iodate via a single intraperitoneal injection in mice leads to the rapid disappearance of the RPE layer within a short timeframe of 1–2 days [42]. The precise chemical process behind this is not fully understood, but it selectively affects RPE cells. Shortly after RPE cells are depleted, the outer segment of the retina's photoreceptors undergoes degeneration, a well-documented observation that signifies the early impact of RPE on photoreceptors. The growth of photoreceptors relies on glucose transport across the RPE, facilitated by membrane transport proteins. The basal-

lateral and apical plasma membranes of RPE cells are abundant in GLUT-1 glucose transporters. Research indicates that in areas where RPE cells exhibit GLUT-1, photoreceptors are robust and elongated, whereas in regions where GLUT-1 expression is inhibited, the underlying photoreceptors develop slowly [43].

The decline of rod cells is paralleled by the deterioration of cone cells, which are both pivotal in capturing light and initiating the process of signal transduction. This process subsequently modulates synaptic transmission to neurons that follow in the visual pathway. Although these cells share a fundamental role in vision, they exhibit distinct genetic profiles that endow them with unique response characteristics and sensitivities to light. Mutations in certain genes specific to rod cells can lead to their toxicity, a phenomenon that in humans can manifest as Retinitis Pigmentosa (RP), a group of disorders marked by the degeneration of rod cells. Interestingly, even though cone cells are not directly affected by these mutations, they too undergo a loss of their outer segments and eventual degeneration following the demise of rod cells [44]. This secondary loss is attributed to the disruption of the glucose supply, suggesting that cone cell degeneration is a consequence of nutritional deprivation [45].

A protein known as Rod-derived Cone Viability Factor (RdCVF), which is secreted by rod cells, has been identified as crucial for the survival and functionality of cone cells [46]. RdCVF interacts with cone cells by binding to them and activating a scaffold protein that helps maintain the stability of GLUT-1 on the cell membrane [47,48]. This implies that the degeneration of rod cells could indirectly affect cone cells by reducing their access to RdCVF and, consequently, their ability to absorb glucose.

Furthermore, alterations in the metabolic processes of rod cells have repercussions for the Retinal Pigment Epithelium (RPE). AMP-activated protein kinase (AMPK), which functions as an intracellular energy sensor, is responsible for regulating the expression of metabolic enzymes [49]. In mice models where AMPK expression is suppressed, the RPE does not show immediate effects [50]. However, over time, rod photoreceptors exhibit mitochondrial fragmentation and a decline in metabolic activity. This metabolic disruption in the retina has a knock-on effect on the RPE, causing an accumulation of vesicles, lipid droplets, and undigested remnants from the outer segments. Additionally, the density of rod cells in the retina influences their size; experiments in mice have shown that at lower densities, rod outer segments are shorter, while at higher densities, they are longer [51], indicating that the density of rod cells can modulate the RPE's ability to deliver nutrients to the retina.

5. Metabolic Changes in Retinal Photoreceptor Cells under Photodamage

The retina is the most susceptible part of the eye to photic damage (the key differences between photic and thermal damage are summarized in Table 1). Exposure to intense illumination for a short duration can lead to acute thermal damage. Conversely, prolonged exposure to light may induce chemical alterations within retinal cells, culminating in cellular demise [52]. Studies have confirmed that natural visible light is a major risk factor for damaging the structure and function of retinal cells, especially high-energy short-wavelength light such as blue light, which can disrupt specific molecular bonds in cells and lead to photochemical damage to the retina [53]. Long-term excessive exposure to bright light can significantly increase the production of reactive oxygen species (ROS), leading to apoptosis of photoreceptor cells and retinal pigment epithelium cells (RPE), endoplasmic reticulum stress, inflammation, visual function impairment, and even macular degeneration.

Table 1. Comparison of thermal and photodamage.

Item	Thermal Damage	Photodamage
Exposure duration	μs–10 s	>1 s
Wavelength	all types	$\lambda < 600$ nm
Minimal lesion size	<beam diameter	=beam diameter
Temperature change	>20 °C temperature ↑	<10 °C temperature ↑
Scotoma	irreparable	reparable

5.1. The Relationship between Mitochondria and Photoreceptor Photodamage

The substantial energy required for vision formation is primarily supplied by mitochondria, which are abundant in the axons of retinal ganglion cells (RGC), the inner segments of retinal photoreceptor cells, retinal glial cells, and RPE [54]. Excessive light exposure can cause irreversible damage to retinal cells, with mitochondrial swelling and nuclear disappearance in photoreceptor cells being the main early manifestations of acute photic damage to the retina [55]. Long-term exposure to blue light can lead to extensive retinal damage. Mitochondria not only regulate energy production but also perform other physiological functions, such as regulating Ca^{2+} levels, redox status, and inducing cell apoptosis through the activation of the MPTP [56].

5.1.1. Oxidative Stress and Photodamage

ROS primarily originate from mitochondria, and if their levels exceed the cell's antioxidant capacity, oxidative stress (OS) occurs, mediating molecular damage to nucleic acids, lipids, and proteins, reducing cellular metabolism and vitality, and even inducing necrosis or apoptosis. It can also lead to Ca^{2+} homeostasis disruption, mitochondrial respiratory chain dysfunction, changes in membrane permeability, mutations in mtDNA, and damage to defense systems [57]. Lipid radicals formed from ROS and singlet oxygen can attack photoreceptor cells and cause damage [58]. Researchers have found that ROS in photoreceptor cells significantly increase after exposure to light using fluorescence probe labeling in live mice [59]. Docosahexaenoic acid (DHA), which is abundant in photoreceptor cells, is susceptible to ROS oxidation, forming other complex products that damage the retina [60]. Injecting the oxidation products of DHA into the mouse retina can promote retinal degeneration, whereas knocking out DHA can inhibit light-induced retinal damage [61]. Additionally, animal studies that inhibit photic damage have also proven that ROS play a key role in retinal photic damage, and the synthetic antioxidant N,N'-Dimethylthiourea (DMTU) can prevent and reduce retinal photic damage in experimental rats [62]. Using the antioxidant lipoic acid in an acute photic damage mouse model can significantly reduce the number of light-induced photoreceptor cell apoptosis and damage to retinal function [63]. In summary, excessive light exposure (especially high-energy short-wavelength light such as blue light) mainly leads to ROS accumulation and oxidative stress damage, thereby affecting the structure and function of retinal mitochondria and ultimately triggering mitochondria-related cell death.

5.1.2. Calcium (Ca^{2+}) Homeostasis and Photodamage

Changes in intracellular Ca^{2+} concentration can affect ATP synthesis, the opening of MPTP, and cytoplasmic Ca^{2+} homeostasis. Under normal light exposure, rhodopsin in rod cells is extensively degraded, activating G proteins, leading to a decrease in cGMP and Ca^{2+} influx. However, excessive light exposure can cause an increase in Ca^{2+} influx [64]. Evidence found that the amount of Ca^{2+} in photoreceptor cells significantly increased under blue light stimulation [65], suggesting that it may be caused by inositol triphosphate (IP3) promoting the release of Ca^{2+} into the cytoplasm. The increase in Ca^{2+} concentration in photoreceptor cells induced by light exposure can activate members of the Ca^{2+} protease (calpains) family and ultimately activate caspase12 to mediate cell apoptosis [66]. The pro-apoptotic protein Bid is cleaved into tBid by calpains, and tBid can promote the formation of Bax homopolymers and mitochondrial membrane permeabilization, leading to the release of cytochrome c (Cyt c) and apoptosis-inducing factor (AIF) from the mitochondrial membrane space, resulting in apoptosis of retinal photoreceptor cells [67]. Therefore, the disruption of mitochondrial Ca^{2+} homeostasis plays an important role in retinal photic damage, and maintaining Ca^{2+} balance will be one of the effective ways to treat retinal photic damage.

5.2. Rhodopsin-Mediated Photodamage

Rod and cone cells express different proteins and pigments. To explore which cells are mainly affected by light damage, researchers briefly exposed Abca4(-/-) Rdh8(-/-) mice [68], which have many characteristics of human retinal degeneration, to intense light. Double quantum microscopy can observe more visual pigment-derived fluorescent groups, expansion of rod cell outer segments, and macrophage infiltration, indicating that rod cells are the main sites of toxic opsin accumulation and degeneration in mouse retinal lesions. Another mouse model lacking functional rhodopsin are also used [69], suggesting that rhodopsin in rod cells is the main medium for light-induced damage. Opsins and the chromophore group of retinaldehyde form rhodopsin. Opsins obtain light through their covalently bound pigment group 11-cis retinal (11CR). When exposed to light, 11CR is converted to all-trans retinal (ATR), a process that generates oxygen radicals, attacking unsaturated fatty acids in the outer segments of the membrane discs. At the same time, opsins are activated, and the ATR clearance mechanism composed of retinaldehyde dehydrogenase, RPE cell proteins, lecithin retinol acyltransferase, and ATP-binding transporter A4 is activated, releasing all ATR, which is converted to 11CR in the RPE [70]. Dysfunction in the regeneration process of 11CR can lead to the accumulation of ATR in the retina, thereby causing cell toxicity reactions and pathological changes mediated by ATR. Animal experiments have shown that the accumulation and photodegradation of ATR can lead to diseases such as AMD, Stargardt disease, acute light-induced retinal lesions, and night blindness [71].

5.3. Inflammation and Photodamage

Inflammation is one of the host defense reactions in innate immunity and is involved in both acute and chronic retinal light damage processes. After short-term exposure to intense light in rabbits, pro-inflammatory cytokines

such as IL-1β and TNF-α were found to be significantly upregulated. Since the retina has immune activity, chronic inflammation induced by long-term light exposure can also induce photoreceptor cell death [72]. Studies have found that when RPE is exposed to light for a long time, the excessive production of ROS can initiate inflammation through pattern recognition receptors (PRRs) and secrete a large number of inflammatory factors such as IL-1β and IL-6, which accumulate in photoreceptor cells and regulate photoreceptor cell apoptosis through caspase-dependent apoptotic pathways [73].

In addition, photoreceptor cells in the light-induced retinal damage mouse model also show characteristics of pyroptosis. After 2 h of light exposure, pyroptosis-related proteins NF-κB, NLRP3, and IL-1β significantly increased and were upregulated with the extension of light exposure time [74,75]. Current research suggests that multiple inflammatory factors and cellular pathways are involved in acute and chronic inflammatory responses and cause light damage to retinal photoreceptor cells through inducing cell apoptosis or pyroptosis. Therefore, the regulation of the release of inflammatory factors and their mediated pathways will help improve the inflammatory microenvironment of the retina and reduce light damage to retinal cells.

6. Key Signaling Pathways in Photoreceptor Cell Damage

In the context of retinal photoreceptor cells' response to light damage and other pathologies, several signaling pathways are of great significance. The PI3K-Akt pathway is vital for maintaining cell viability and metabolic equilibrium. When exposed to light damage stimuli, cell surface receptors like the insulin—like growth factor receptor (IGF-1R) can trigger PI3K activation. PI3K then phosphorylates phosphatidylinositol-4,5-bisphosphate (PIP2) to form phosphatidylinositol-3,4,5-trisphosphate (PIP3). As a second messenger, PIP3 recruits and activates Akt. Subsequently, activated Akt phosphorylates downstream target proteins such as Bad. Phosphorylated Bad binds to 14-3-3 protein, preventing its combination with Bcl-2 or Bcl-XL and thus inhibiting apoptosis. Moreover, Akt can activate the mammalian target of rapamycin (mTOR) pathway by phosphorylating tuberous sclerosis complex 2 (TSC2), promoting protein synthesis and cellular repair after light damage.

The MAPK signaling pathway, encompassing sub-pathways like ERK, JNK, and p38, also plays a crucial part. In light-induced oxidative stress and inflammation, reactive oxygen species (ROS) in cells can activate the MAPK pathway. For instance, ROS can activate JNK kinase, which in turn phosphorylates transcription factors like c-Jun. This leads to the upregulation of pro-apoptotic genes such as Bax, promoting cell death. Meanwhile, activation of the p38 MAPK pathway can cause cell cycle arrest, suppressing cell proliferation and reducing the metabolic burden of damaged cells, prompting them to repair or undergo apoptosis if repair is not possible. The ERK pathway, when moderately activated, can facilitate cell survival by phosphorylating transcription factors like Elk-1 to regulate the expression of cell cycle-related and anti-apoptotic genes. However, excessive or persistent activation of ERK may result in abnormal cell proliferation or disrupted apoptosis balance, exacerbating retinal lesions.

In age-related macular degeneration, the activation of oxidative stress-related signaling pathways is a key link. A large amount of ROS generated during the metabolic process of retinal pigment epithelial cells (RPE) and photoreceptor cells can activate the NF-κB signaling pathway. ROS phosphorylates IκB protein by IκB kinase (IKK), resulting in the degradation of IκB protein, releasing the NF-κB dimer and translocating it into the nucleus, activating the expression of a series of inflammation-related genes such as interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α). These inflammatory factors further recruit immune cells, triggering a chronic inflammatory response, aggravating the oxidative damage and cell apoptosis of the retina, forming a vicious cycle and accelerating the development of age-related macular degeneration. This indicates that the NF-κB signaling pathway plays an important role in mediating the connection between oxidative stress and inflammatory response, providing a potential intervention target for the treatment of this disease.

In conclusion, in-depth research on the mechanism of these signaling pathways in retinal photoreceptor cell diseases is helpful for developing new treatment strategies for retinal diseases. By regulating the activity of signaling pathways to intervene in cell metabolism and function, the progression of diseases can be delayed or prevented.

7. Photoreceptor Cell Metabolism in Retinal Disease Pathogenesis

7.1. Diabetic Retinopathy

Diabetic retinopathy (DR) is the most common and severe microvascular complication of diabetes. It is a chronic progressive condition caused by diabetes that leads to leakage and obstruction of the retinal microvasculature, resulting in a range of fundus lesions such as microaneurysms, hard exudates, cotton wool spots,

neovascularization, vitreous proliferation, macular edema, and even retinal detachment [76,77]. Figure 3 illustrates the ocular conditions associated with diabetic retinopathy (DR) onset. It has long been considered a vascular disease, but recent research has revealed abnormalities in the neural retina as well.

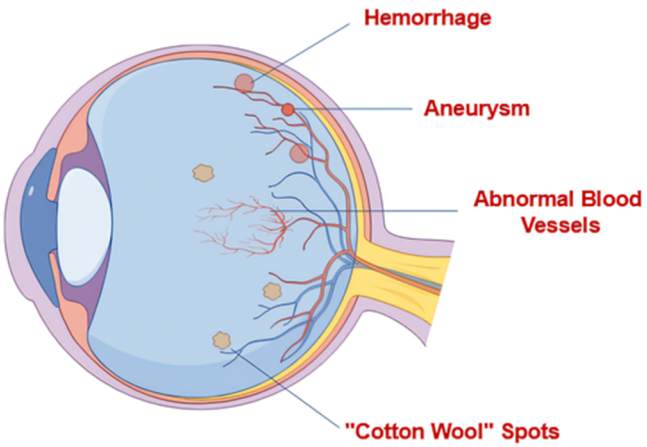

Figure 3. Diabetic Retinopathy Pattern Diagram.

7.1.1. Enhanced Retinal Oxidative Stress

The onset of diabetes is associated with heightened oxidative stress within the retina [78–80], which significantly influences the progression of diabetic retinopathy (DR). Laboratory investigations have revealed that while endothelial, pericyte, and Müller cells contribute to superoxide generation, their impact is minor in comparison to the oxidative stress emanating from photoreceptors during the early stages of diabetes [79,81]. Although white blood cells in the diabetic retina could potentially raise superoxide levels, staining techniques using dihydrofluorescein or dihydroethidium on retinal sections have demonstrated that photoreceptors are the predominant source of oxidative stress in diabetic conditions [79,82]. This is further supported by the observation that the rise in superoxides is mitigated in retinas with photoreceptors lacking opsin or those that have been chemically degraded by iodoacetic acid [79]. Moreover, under diabetic conditions or in cases of degeneration, such as in opsin-deficient rodent models, photoreceptors are found to generate superoxides at elevated levels [83].

7.1.2. Photoreceptor-Mediated Inflammation

Recent findings indicate that photoreceptor cells are involved in the escalation of inflammatory proteins within the diabetic retina [84], acting as a source of increased inflammatory mediators, including IL-1α, IL-1β, IL-6, IL-12, CXCL1, MCP-1, CXCL12a, I-309, CCL25, and TNF-α [85]. Studies have identified photoreceptors as a source of IL-1β and its receptors in diabetic retinal environments [86]. The inflammatory response within photoreceptors may be modulated by NF-κB signaling, which is activated in 661W cells under diabetic-like conditions [87]. TAK1 and NADPH oxidase have been implicated in the activation of NF-κB signaling and the subsequent release of inflammatory mediators in these cells under high glucose conditions [85,88].

7.1.3. Ionic Flux

The influx of ions into photoreceptor cells is essential for vision-related processes, and diabetes can disrupt these mechanisms [89]. There is evidence of a decrease in the activity of enzymes that regulate ion movement, such as calcium ATPase and Na/K-ATPase in the retina and RPE, due to the effects of diabetes [90–92]. Given the prevalence of photoreceptor cells in the retina, it is plausible that they account for the majority of the diabetes-induced reduction in Na/K-ATPase activity, although this has yet to be confirmed. It has been observed that antioxidants, lipoic acid, catalase, the absence of iNOS, or daily short sessions of far-red light photobiomodulation can prevent diabetes-induced defects in ion entry into photoreceptor cells [93–95].

7.1.4. Oxygen Deprivation

Photoreceptor cells, with their high mitochondrial content in the inner segments, are the primary consumers of oxygen in the retina [96], particularly in the dark when the rod dark current is most active [97,98]. HIF-1α, a key regulator of cellular responses to hypoxia, is activated during hypoxic conditions and has been found to increase in photoreceptors and other retinal layers in diabetic states [99,100]. While HIF-1α is linked to hypoxia-induced abnormalities in DR, the specific contribution of the outer retina to HIF-1α-mediated processes remains to be fully understood.

7.2. Retinitis Pigmentosa

Retinitis Pigmentosa (RP) is a group of genetically heterogeneous disorders primarily characterized by the death of photoreceptor cells. Clinical manifestations include night blindness, progressive loss of vision, and a progressive constriction of the visual field, along with abnormal electroretinograms [101]. Numerous gene defects associated with RP have been identified, leading to a gradual loss of function in the rod cells of RP patients, followed by an impairment of the photopic function of cone cells, ultimately resulting in complete blindness [102].

Current research has confirmed the presence of gene mutations encoding transcription factors and post-transcriptional RNA modification factors in RP patients, such as the precursor messenger RNA splicing factor (RPPF) [103]. The NRL and CRX genes encode transcription factors, and mutations in these genes can lead to the development of RP [104]. Specifically, mutations in the NRL gene can cause a dysfunction in the synthesis of rhodopsin within cells; mutations in the CRX gene not only block the transport of proteins into the nucleus of photoreceptor cells [105], but also affect the binding of CRX to NRL to some extent, thereby causing a disruption in the transcription function of certain proteins within photoreceptor cells [106].

The RHO gene encodes a 348-amino acid opsin protein, which binds with retinal to form RHO. The proline at position 347 is located at the end of the opsin molecule, and a mutation at this site can alter the amino acid sequence related to opsin transport. This alteration can further disrupt the normal metabolism of opsin, causing it to accumulate within the rod cells and preventing its transport to the outer segment disc membrane. Consequently, this leads to metabolic dysfunction of the retina and triggers RP.

7.3. Age-Related Macular Degeneration

Age-Related Macular Degeneration (ARMD) is a progressive and irreversible loss of central vision associated with aging, characterized by the formation of drusen, thickening of the Bruch's membrane, damage to the retinal pigment epithelium (RPE) and photoreceptor cells, and the growth of choroidal neovascularization in the macular region [107]. ARMD is one of the leading causes of central vision loss in the elderly. In the early stages of ARMD, metabolic changes may lead to dysfunction of the RPE and photoreceptor cells, subsequently affecting vision.

It is posited that oxidative stress and damage occurring in retinal cells contribute to the development of ARMD [108]. RPE and photoreceptor cells require high levels of oxygen and other nutrients to perform metabolic functions such as phagocytosis, thus generating a significant amount of ROS. Since RPE cells are terminally differentiated and cannot regenerate after damage, a decrease in RPE cell density leads to impaired metabolic and phagocytic functions of photoreceptor outer segments. This results in the accumulation of ROS, causing oxidative damage [109], and ultimately making the retina, where RPE and photoreceptor cells aggregate, the most severely affected area by ocular oxidative stress reactions [110], leading to the onset of ARMD.

7.4. Metabolic-Based Therapeutic Approaches

Harnessing the eye's metabolic environment to enhance the resilience of photoreceptors and RPE against stress presents a promising approach for managing a variety of genetically diverse diseases.

7.4.1. DR and ARMD

Nutritional intake significantly influences the health of the retina. Research indicates that mice consuming a diet rich in fats are prone to a specific type of retinal degeneration. Furthermore, mice lacking Nrf2, a protein crucial for maintaining redox balance, show signs of RPE atrophy and retinal degeneration when exposed to diets high in glucose levels [111].

Vitamins have a multifaceted impact on DR, leveraging their antioxidant and anti-inflammatory capabilities. Supplementing the diet with vitamins C and E, along with other antioxidants, can counteract the oxidative stress, protein kinase C activation, and nitric oxide accumulation in the retina caused by elevated blood sugar levels [112].

This strategy is also instrumental in preventing early microvascular damage associated with DR. The sustained intake of these antioxidants can prevent the progression of DR in its early stages. Additionally, incorporating the antioxidant N-acetyl cysteine into the diet may mitigate the loss of cone cells following rod cell degeneration [113]. High levels of iron and bisretinoids can induce oxidative damage, but this can be mitigated by the use of iron chelators. The inclusion of docosahexaenoic acid, a fatty acid abundant in photoreceptors, in the diet offers neuroprotective advantages. The composition of the gut microbiome, influenced by diet, may also play a role in the risk of ARMD.

Epigenetic regulation, largely governed by DNA methyltransferase 1 (DNMT1), is essential for preserving the epigenetic state. Elevated DNMT1 levels in diabetic retinal cells correlate with hypermethylation of the D-loop region in mitochondrial DNA (mtDNA), resulting in increased 5-methylcytosine (5 mC) levels [114]. Such hypermethylation can interfere with genes that encode for the electron transport chain (ETC), potentially triggering a cycle of increased superoxide radical production and worsening DR. The use of pharmaceuticals like 5-aza-2′-deoxycytidine, an FDA-approved DNMT inhibitor, could help maintain redox balance and prevent the progression of DR.

Current research in animal models is exploring strategies to enhance the stress resilience of photoreceptors by modulating their metabolic pathways. This includes strategies such as overexpressing TGF-β1 and RdCVF, as well as the targeted elimination of SIRT6 and PKM2 [115]. The objective of these approaches is to improve the resistance of photoreceptors to metabolic stress, thereby reducing the likelihood of degeneration.

7.4.2. Retinitis Pigmentosa

RP is a genetically diverse condition with varied phenotypic expressions due to numerous pathogenic mutations, which ultimately result in the degeneration of the RPE and the subsequent apoptosis of photoreceptors, causing retinal damage. Neuroprotective strategies represent an early and extensively utilized treatment modality for RP, known for its favorable safety profile and minimal adverse effects. These therapies are often initiated during the initial stages of the disease and can be effectively integrated as a complementary treatment in later phases as well. Several common neuroprotective agents and their functions are summarized in Table 2. Additionally, various other common therapeutic approaches along with their advantages and disadvantages are presented in Table 3.

Table 2. Common Neuroprotective Agents and Functions in RP.

Neuroprotective Agent	Capacity
CNTF	1. Promote the survival of photoreceptor cells; 2. Activate the mTOR pathway in neurons to promote axonal regeneration; 3. PirB in Müller cells affects the regeneration of RGC neurites; 4. Induce neuroinflammatory responses.
BDNF	1. Inhibit autophagy and enhances synaptic plasticity; 2. Activate Protein Kinase C (PKC) to promote synaptic plasticity.
FGF	Involvement in GLP-1 receptor signaling transduction helps regulate fatty acid oxidation, mitochondrial integrity, and function.
DHA	1. Stimulates the production of intrinsic antioxidants and initiates selective autophagy of misfolded proteins; 2. Adiponectin receptor 1 maintains docosahexaenoic acid levels and supports the survival of photoreceptor cells.
VPA	Stimulate the restoration of retinal health in conditions of degeneration by managing SOX2 levels in fetal RPE stem-like cells.

Table 3. Other Common Therapies in RP.

Therapy	Mechanism	Advantages	Disadvantages
Vitamin A	Maintain the visual pathway.	Low cost and easy to operate.	Low therapeutic efficacy and teratogenicity at high doses.
Stem Cell Therapy	Replace non-functional retinal cells and supply growth factors.	Good safety and effective results.	Involves ethical issues with embryonic stem cells, a limited number of clinical samples, and relatively high operational difficulty.

Gene Therapy	Repair mutated genes.	Abundant clinical experience and high safety.	The duration of therapeutic effect is relatively short.

8. Prospects for Research on Photoreceptor Cell Metabolism

The retina, serving as a key structure in vision formation, is a highly specialized tissue with a unique structure and adaptability. As the sole cells within the retina capable of detecting light stimuli, the significance of retinal photoreceptor cells is undeniable. Given their specific location, structure, and surrounding environment, the metabolism of retinal photoreceptor cells differs from that of other tissues. Research into these unique aspects will contribute to a deeper understanding of the pathophysiological processes involved in the diseases of retinal photoreceptor cells.

Retinal light damage is a critical factor in the pathogenesis of many retinal diseases, and a comprehensive understanding of its mechanisms is essential for targeted prevention and treatment. Both retinal light damage and systemic diseases such as diabetes have a profound impact on the metabolism and function of retinal photoreceptor cells. These issues are gaining increased attention and are expected to remain a focal point of research in the future.

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