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General Pathophysiology in Retinal Degeneration

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Abstract

Retinal degeneration, including that seen in age-related macular degeneration and retinitis pigmentosa (RP), is the most common form of neural degenerative disease in the world. There is great genetic and allelic heterogeneity of the various retinal dystrophies. Classifications of these diseases can be ambiguous, as there are similar clinical presentations in retinal degenerations arising from different genetic mechanisms. As would be expected, alterations in the activity of the phototransduction cascade, such as changes affecting the renewal and shedding of the photoreceptor OS, visual transduction, and/ or retinol metabolism have a great impact on the health of the retina. Mutations within any of the molecules responsible for these visual processes cause several types of retinal and retinal pigment epithelium degenerative diseases. Apoptosis has been implicated in the rod cell loss seen in a mouse model of RP, but the precise mechanisms that connect the activation of these pathways to the loss of phosphodiesterase (PDE6 β) function has yet to be defined. Additionally, the activation of apoptosis by CCAAT/-enhancer-binding protein homologous protein (CHOP), after activation of the unfolded protein response pathway, may be responsible for cell death, although the mechanism remains unknown. However, the mechanisms of cell death after loss of function of PDE6, which is a commonly studied mammalian model in research, may be generalizable to loss of function of different key proteins involved in the phototransduction cascade.

Brief Overview of the Eye

The eye is a complex organ that provides information on the form, light intensity, and color reflected from objects. It is divided into two segments: anterior and posterior. The anterior segment consists of the cornea, lens, iris and ciliary body, and the posterior segment consists mainly of the vitreous, retina, and choroid [1]. The sclera and cornea constitute outer

protective layers of the eye. The choroid, ciliary body and iris comprise the uveal tract. The choroid is a vascular layer that supplies the outer one third of the retina and the retinal pigment epithelium (RPE). The ciliary body produces aqueous humor and regulates the contour of the crystalline lens. The retina is the neural sensory layer [2, 3]. The focus in this chapter will be the retina and RPE.

Retina and Retinal Pigment Epithelium

In situ, RPE cells are organized as a monolayer, whose shape ranges from cuboidal in the periphery to columnar under the macula. RPE cells provide nourishment (e.g. vitamin A metabolites) and clear outer segment (OS) debris (via daily phagocytosis of OS tips) of the overlying photoreceptor cells [4–8]. RPE cells are polarized, with the apical region expressing microvilli that interdigitate with photoreceptor OS and the basal region expressing specific transport enzymes. The ion transporters and tight junctions between adjacent RPE cells allow for control of intercellular communication and electrical potential differences between the two surfaces of the epithelium. In this way, RPE cells help to regulate the composition (e.g. pH) of the photoreceptor extracellular matrix and also create a selective permeability barrier known as the outer blood-retinal barrier [3].

The sensory retina contains at least 15 different types of neurons that form at least 38 distinct synapses with one another [3]. There is an outer layer of light-sensitive neurons, called the photoreceptor cells, that make synapses with secondorder neurons known as bipolar cells. Bipolar cells in turn make synapses with the ganglion cells, whose axons comprise the nerve fiber layer and optic nerve. Horizontal cells are neurons that make synaptic connections with bipolar and photoreceptor cells, and amacrine cells are neurons that make synaptic connections with bipolar and ganglion cells. In pathological states, these synaptic arrangements can become disordered. Müller cells are glial cells that span the entire width of the retina. The inner limiting member of the retina is the basement membrane of the Müller cells. The outer limiting membrane comprises junctional complexes between the Müller cells and photoreceptors (fig. 1). Photons pass through the translucent retina and cause a conformational change in the visual pigment, rhodopsin (RHO), which results in activation of a chemical cascade that ultimately results in ganglion cell action potential formation. Action potentials are conducted from the optic nerve to the lateral geniculate nucleus and other relay centers (e.g. suprachiasmatic nucleus) as well as to the visual cortex in the occipital lobe and, ultimately, to associated parietal cortex. Stray light is absorbed by the melanin-containing RPE.

The photoreceptor cells consist of an OS, an inner segment (IS), a cell body, and a synaptic terminal for neurotransmission to the second-order cells of the retina. The photoreceptor layer is composed of two specific types of photosensitive cells, rods and cones. The rod cells comprise approximately 97% of the retinal photoreceptors, and the cone cells comprise the remaining 3% of the retinal photoreceptor cells in both mouse and human retinæ. The IS of both photoreceptor cell types contains ribosomes, mitochondria, and membranes that are used to assemble and transport opsin molecules to the OS discs [9]. In the rods, the OS is characterized by invaginations of the plasma membrane at its base, which makes detached stacks of disc structures [9]. Within the cones, on the other hand, the discs remain attached

to the OS membrane. The apical microvilli of RPE cells envelop the OSs of rods and cones and separate the distal discs from the remaining stack. These shed discs are phagocytosed and degraded within the RPE. Since the photoreceptors constantly produce OSs, RPE phagocytosis of the OS tips enables the photoreceptor cell OS length to be stable [9–11]. This process of OS disc renewal is circadian and occurs daily (in the morning for rods and in the evening for cones) in mammals.

Each photoreceptor cell has a specific role for the type and amount of light that leads to its signaling response. Rods are highly sensitive photoreceptors that respond to single photons of light. Therefore, they are active in dim-light settings and allow for night vision. Rods have a response range of three orders of magnitude, up to 10,000 photons per second (mesopic vision), at which point they saturate [12]. When the rods saturate, the cones begin to respond (photopic vision). By shifting their operating curves, cones take the human eye out to 10 billion photons per second (as can be seen during the noon sun on freshly fallen snow at altitude). There are different types of cone cells, each responsible for sensing different wavelengths of light and therefore allowing for day-time and color vision. In humans, there are three types of cone cells: the S-cones, L-cones, and M-cones. The macula, a central region of the retina, is enriched in cone cells, causing the cones to be responsible for the central visual field while the rods underlie the majority of the peripheral visual field responses [12, 13].

As noted above, the retina transduces various aspects of the optical properties of the image of regard into neural signals, and these coded neural signals are then transmitted to the visual cortex. Retinal circuits transform patterns of light and darkness on the photoreceptor mosaic of the retina, and these patterns lead to repetitive discharges from a two-dimensional array of ganglion cells to the brain. Over the past years, progress has been made in understanding the mechanisms of neurocircuitry and phototransduction in the retina.

Phototransduction Cascade

Each OS disc contains several million opsin molecules [14]. In the dark, each opsin protein is non-covalently coupled with a vitamin A derivative, 11-*cis*-retinal, in the OS disc to form RHO. As noted below, photon absorption results in isomerization of 11-*cis* to all-*trans* retinal, with dissociation of the dimer into opsin and all-*trans*-retinal. In the dark, there is a circulating current that flows from the IS to the OS of the photoreceptor cell. After light exposure, a process known as the phototransduction cascade is initiated, and this interrupts the cell current. This cascade occurs in the OS discs. As described in greater detail below, the phototransduction cascade leads to altered cyclic guanosine monophosphate (cGMP) levels in the photoreceptor OS. This change in cGMP levels transmits the light response signal from the OS discs to the plasma membrane of the photoreceptor cell [15]. This process is carefully regulated by various molecules, each of which is responsible for the activation, deactivation, and adaptation of the phototransduction cascade in the photoreceptor cell.

RHO is a seven-loop transmembrane G-protein-coupled receptor that contains a protonated Schiff base with a lysine side chain. This lysine side chain is covalently linked to the 11-*cis*

retinal chromophore [16, 17]. Within the RPE cells, stored all-*trans* retinal is isomerized to 11-*cis* retinal by retinal pigment epithelial 65-kDa (RPE65) protein. 11-*cis* retinal then passes out of the RPE and into the OS of the photoreceptor cell to bind to opsin and make RHO. Light causes RHO to undergo a conformational change to an activated state, called metarhodopsin II (Rh*). Rh* activates hundreds of transducin molecules ($G_{\alpha\beta\gamma}$). $G_{\alpha\beta\gamma}$ are heterotrimeric G-proteins that act by exchanging guanosine diphosphate for guanosine triphosphate (GTP) [18]. This activation by Rh* causes GTP to bind to the G_{α} subunit of $G_{\alpha\beta\gamma}$, and this G_{α} -GTP then dissociates from the $G_{\beta\gamma}$ portions of $G_{\alpha\beta\gamma}$. After dissociation, the G_{α} -GTP binds to the inhibitory γ -subunits of cGMP-phosphodiesterase 6 (PDE6) [19].

In rods, PDE6 is a heterotetrameric protein consisting of a catalytic α -subunit, a catalytic β -subunit, and two inhibitory γ -subunits. In cones, PDE6 consists of a catalytic dimer that contains two identical α '-subunits, rather than the α - and β -subunits found in the rod cell. Additionally, the γ '-inhibitory subunits of the cone PDE6 differ slightly in size and amino acid composition from the rod γ -inhibitory PDE6 subunits [16]. PDE6 is highly important in the phototransduction cascade, as it is the primary regulator of cytoplasmic cGMP concentration in the photoreceptor cells. In the dark, PDE6 is in an inactive form, with the γ -inhibitory subunits bound (PDE6 $\alpha\beta\gamma$), and cGMP levels within the photoreceptor cell OS are high (micromolar range) [15]. As a result, cGMP-gated $\text{Na}^+/\text{Ca}^{2+}$ ion (CNG) channels within the plasma membrane remain open, allowing a current to circulate through the photoreceptor cell (fig. 2a).

After light stimulation of the phototransduction cascade, the binding of G_{α} -GTP on the γ -subunits of PDE6 removes the inhibition on the catalytic α - and β -subunits of PDE6 [18–20]. The activated PDE6 hydrolyzes cGMP, breaking it down and reducing its concentration within the photoreceptor cell [21]. The cGMP concentration is thus present in two separate pools: free and bound to noncatalytic cGMP-binding sites of the phototransduction effector enzyme PDE6. PDE6-bound cGMP makes up approximately 90% of the total cGMP content in the photoreceptor; however, its role remains uncertain. What is known is that this light-activated PDE is approximately 300 times more active than in its basal state, rapidly breaking down the cyclic nucleotide levels [22]. The rapid reduction of cGMP within the photoreceptor cell after light stimulation of the phototransduction cascade causes the CNG channels located on the plasma membrane to close (fig. 2b). Therefore, the levels of Na^+ and Ca^{2+} in the cytoplasm are reduced, causing the rod cell to become hyperpolarized. Hyperpolarization of the rod cell causes it to decrease glutamate release from its synaptic terminal (in the outer plexiform layer), which alters synaptic signaling downstream in the bipolar and ganglion cells.

After light stimulation, the phototransduction cascade has to undergo deactivation in order to return cGMP to its basal levels. The photoexcited Rh* is inactivated by the phosphorylation of threonine and serine residues at its carboxyl tail by a RHO-specific kinase called G protein-dependent receptor kinase I (GRK1) [9]. This phosphorylated RHO (Rh*-P) binds relatively efficiently to a molecule called arrestin (Arr; also called S-antigen) and less efficiently to G_{α} . Arr acts on the Rh*-P by inhibiting the removal of the phosphate groups [23]. This rapidly reduces the amount of dephosphorylated, active Rh* available for the activation of G_{α} and the rest of the phototransduction cascade.

Additionally, $G_{t\alpha}$ has intrinsic GTPase activity to inactivate itself after its binding to the γ -inhibitory subunits of PDE6 [22]. The PDE6 $\alpha\beta$ catalytic subunits reassociate with the two PDE6 γ subunits for inactivation of the PDE6 complex, while retinal guanylate cyclases (Ret GC-1 and Ret GC-2) become activated and catalyze cGMP synthesis in the photoreceptor cell [9]. The return of the basal cGMP concentration in the photoreceptor cell reopens the CNG channels, which completes the deactivation process. Activation of the phototransduction cascade starts again when Rh*-P-Arr binds to 11-*cis* retinal, which causes Arr dissociation. The Rh*-P is then dephosphorylated by phosphatase 2A, and the light/dark activation/deactivation cycle can continue within the photoreceptor cell.

In addition to reacting to light through activation of the phototransduction cascade, photoreceptors adapt to constant light stimulation. As previously mentioned, light stimulation of the phototransduction cascade leads to the closure of the CNG channels in the photoreceptor OS, and, in turn, a decline in Ca^{2+} influx into the cell. Intracellular Ca^{2+} levels act to inhibit the guanylate cyclases (Ret GC-1 and Ret GC-2). Therefore, Ret GC-1 and Ret GC-2 are activated when light stimulates the phototransduction cascade and Ca^{2+} levels decrease within the cell [24–26]. This phenomenon occurs through the stimulation of Ret GC-1 and Ret GC-2 by the guanylate cyclase-activating proteins (GCAP-1/p-20 and GCAP-2/p24). These guanylate cyclases catalyze the formation of cGMP, which counteracts the reduction in cGMP by PDE6 after the activation of the phototransduction cascade.

Additionally, a molecule called recoverin then mediates the Ca^{2+} sensitivity of GRK1 phosphorylation of Rh*. Thus, prolonged light leads to a reduction in Ca^{2+} levels and induces GRK1 activity by reducing recoverin's inhibition of GRK1. Furthermore, the CNG channel, responsible for the ionic current of the photoresponse, binds a molecule called calmodulin at high levels of Ca^{2+} , and prolonged light reduces calmodulin binding and leads to a decline in the channel affinity for cGMP [27]. As a result, the channel reopens at lower levels of cGMP than it would in dark conditions.

Lastly, light adaptation leads to a greater inhibition of the PDE6 enzyme to allow for a rapid reduction in the hydrolysis of cGMP. Ca^{2+} -sensitive members of the protein kinase C (PKC) family phosphorylate the two PDE6 γ subunits. This phosphorylation site is blocked while the γ -subunits are attached to PDE6 $\alpha\beta$, but light activation of the phototransduction cascade allows for $G_{t\alpha}$ -GTP to release the γ -inhibitory subunits from the PDE6 $\alpha\beta$ complex. After GTP hydrolysis, free PDE6 γ is then phosphorylated by members of the PKC family at threonine 35, which allows it to re-bind to PDE6 $\alpha\beta$ and results in a greater inhibition of the catalytic activity of PDE6.

Alterations in the activity of the phototransduction cascade, such as changes affecting the renewal and shedding of the photoreceptor OSs, visual transduction, and/or retinol metabolism have a great impact on the health of the retina. Mutations within any of the molecules responsible for these visual processes cause several types of retinal and RPE degenerative diseases. The majority of retinal degenerations are caused by gene defects leading to reduced protein levels or incorrect protein functions [4, 9, 28]. For example, the

inability of the RPE to phagocytose the photoreceptor OS causes a form of autosomal recessive retinitis pigmentosa [9, 29].

Retinal Degeneration

Retinal degeneration, including that seen in age-related macular degeneration (AMD) and retinitis pigmentosa (RP), is the most common form of neural degenerative disease in the world [30–32]. The loss of sight affects approximately 3.4 million people in the USA alone and is expected to increase in the future due to the aging of the population of industrialized countries [33]. Visual impairment ranks only behind arthritis and heart disease with respect to disease impact on function in the elderly. In fact, visual loss is often considered by patients to be their dominant health issue, even in the presence of other chronic disabling disorders [34]. Patients exhibit a loss of quality of life as they need assistance in daily tasks such as walking, reading, or driving.

There is great genetic and allelic heterogeneity of the various retinal dystrophies. These diseases have been classified using age at onset, electrophysiological, and psychophysical studies. These classifications can be ambiguous, however, as there are similar clinical presentations in retinal degenerations arising from different genetic mechanisms. For instance, RP can be caused by mutations within components of the phototransduction cascade, such as RHO or PDE6, as well as by mutations within rod OS membrane proteins, such as peripherin [35, 36]. Additionally, different mutant alleles at the same locus can cause varying clinical presentations. For example, mutations within the β -subunit of PDE6 can cause two different retinal degenerative diseases: either congenital stationary night blindness or RP [35, 36]. Currently, the most precise method of classification is based on the specific molecular genetic defect, and genetic testing is becoming a common practice used by clinicians to complement their clinical diagnosis.

Retinitis Pigmentosa

RP is the most common cause of hereditary blindness worldwide, affecting approximately 1:3,000 people [4, 37–40]. The general pathophysiological aspects of RP mimic various other retinal degenerative diseases, and therefore will be discussed in this chapter. Various forms of RP can be classified according to the pattern of inheritance, including autosomal dominant (15–20% of cases), autosomal recessive (20–25% of cases), and X-linked (10–15%). The remaining 40–55% of cases are currently of unclassified inheritance [41, 42]. These unclassified RP patients have a negative family history of RP, and are denoted as simplex RP. The majority of simplex RP cases are believed to be autosomal recessive [42]. Autosomal dominant forms of RP are usually the mildest, with onset that can occur as late as 50 years of age. Autosomal recessive cases, on the other hand, are more severe, and disease onset typically occurs during the first decade of life [43]. Additionally, RP can be associated with other systemic abnormalities (syndromic RP) and is involved in more than 30 disease syndromes. Most forms of syndromic RP present with extraocular abnormalities and are autosomal recessive disorders, such as Usher syndrome (associated with deafness) and Bardet-Biedl syndrome (associated variably with obesity, polydactyly, mental retardation, and infertility) [42].

Genetically, most forms of RP are monogenic, although there have been cases of digenic-diallelic and digenic-triallelic inheritance. Due to RP being both locus heterogeneous and phenotypically heterogeneous, mutations in no single gene are known to cause more than 10% of cases of RP [42]. In 2013, there were 45 genes mapped that cause nonsyndromic forms of RP, although there are probably many more genes responsible for this disease as approximately 200 more genes have already been identified that are involved in retinal disease [44].

In RP, the progressive atrophy of the rod photoreceptor cells leads to the secondary death of the cones. Affected individuals often present with night blindness (nyctalopia) and constricted visual fields (tunnel vision), but central vision (e.g. reading vision, facial recognition) is normal or nearly normal. Eventually central vision is lost as the cone cells degenerate. Occasionally, central visual loss is due to retinal edema (termed cystoid macular edema). Unfortunately, there is no cure for RP, in part because the basic mechanisms causing the rod and cone cell death are not well understood [45]. This photoreceptor cell death has been thought to result from a caspase-dependent apoptotic mechanism [46, 47]. However, other disease pathways, such as calpain-mediated cell death or proteasome activity, may be also responsible for photoreceptor degeneration [9, 48, 49].

Although the mechanism(s) of photoreceptor death are not fully elucidated, RP can be classified into three stages of clinical disease. In stage I of RP, patients present with night blindness. Most patients ignore or are unaware of this symptom, and typically they do not recognize the disease phenotype until the teenage years, when they attend evening events [43]. There are no visual defects present in the daylight, and patients have normal life activities. The electroretinogram, a clinical test that measures the electrical response of the retinal cells to flashes of varying light intensities, will exhibit a loss of visual response at this time [43]. Therefore, at early stages of the disease, most patients with RP will go undiagnosed.

In the mid-stage of RP, patients have difficulty performing most night-time activities, such as driving, and are aware of a loss of their peripheral visual field even in daylight. Additionally, patients may become photophobic, especially in response to diffuse light, such as occurs with cloudy weather [43]. As a result, patients have difficulty reading and performing daily activities. At this stage, patients notice the disease phenotype, visit a clinician, and are diagnosed with RP. At this stage, fundus examination discloses the presence of bone spicule-shaped pigment deposits in the mid-periphery of the retina along with RPE atrophy. Narrowing of the retinal vessels at the optic nerve head is also apparent at this time. Electroretinogram examination shows an attenuated visual response in the cone cells and a complete loss of visual response under scotopic, dark-adapted conditions [43]. The latter condition reflects the loss of the majority of the rods.

In the final stage of RP, the clinical findings that occur in the mid-stage of the disease worsen until the patients have lost their ability to perform daily tasks on their own and may be legally blind (best-corrected visual acuity of 20/200 or worse in the better seeing eye or visual field constricted to 20° or less in the better seeing eye). They will then continue to progress until their central visual field is lost, rendering them blind with no light perception

at all. This disease not only affects the patient and their loved ones but the society as a whole as the cost of caring for these visually handicapped persons for the remainder of their lives is high.

Mechanisms of Degeneration

RP is arguably one of the best models for studying neurodegenerative diseases for three reasons. First of all, the basic pathogenic process in RP, that of rod cell atrophy leading to a secondary, nonautonomous death of the cone cells, is generalizable to other forms of retinal degenerative disease, such as AMD or even normal aging. Secondly, multiple mouse [50–56] and dog [57–59] models now exist with mutations in PDE6 leading to RP, which is the third most common cause of autosomal recessive RP [60]. Third, unlike mouse models of EYS [61] or ABCA4 [62], common photoreceptor degenerative diseases in which the mouse model does not mimic human disease, the mouse models with loss of PDE6 function mimic the human phenotype.

The *Pde6 β^{dl}* mouse has been used extensively as a model of early-onset retinal dystrophy [63, 64]. *Pde6 β^{dl}* is a null allele because it harbors a non-sense mutation in the noncatalytic cGMP-binding domain. Therefore, mutant mice do not express ribonucleic acid (RNA) or protein and do not show any detectable PDE6 activity [65, 66]. *Pde6 β^{dl}* mutants exhibit truncated and disorganized OSs at postnatal day 7 (P7) and complete rod cell loss by P21 [31, 67]. Although the cones do not express PDE6 β , they die approximately 3 weeks after the degeneration of the rods. Thus, cone cell apoptosis, in this context, is nonautonomous [68].

As expected for a loss of function of PDE6, the *Pde6 β^{dl}* mice show abnormal cGMP regulation. Compared to age-matched controls, these mice exhibit dramatic increases in cGMP levels between P10 and P14 and then display a rapid decrease between P16 and P21 [69]. cGMP increases because guanylate cyclase 2D (GUCY2D), which produces cGMP, has normal activity even with a loss of function of PDE6. Since synthesized free cGMP from GUCY2D accumulates and opens the CNG channels, this increase in cGMP is accompanied by high intracellular Na⁺ and Ca²⁺ cation concentrations.

The results found in the analysis of the *Pde6 β^{dl}* mutant mouse model suggest that reduced PDE6 activity contributes directly to (1) defective OS development, (2) the accumulation of excessive free cGMP, and/or (3) the accumulation of excessive intracellular Ca²⁺ [16, 17, 70]. This decrease in PDE6 activity, even if incremental, could cause cGMP and cation concentrations to exceed critical threshold levels above which they will interfere with OS differentiation and/or initiate the unfolded protein response (UPR) and, afterwards, the apoptotic program.

The UPR pathway is induced by misfolded proteins that are retained in the endoplasmic reticulum (ER). Ca²⁺-induced stress on a cell, such as occurs when the CNG channels remain open after light stimulation, can result in protein modifications that can lead to the accumulation of un- or misfolded proteins within the ER [71]. The initiation of the UPR is characterized by the activation of two integral membrane serine-threonine kinases: inositol requiring 1 (IRE1) and pancreatic ER eIF2 α kinase. Additionally, the transcription factor

ATF6 is also involved in initiation of the UPR. The activation of IRE1 results in the up-regulation of the genes that encode the proapoptotic transcription factor C/EBP homologous 68 protein (CHOP) as well as the ER chaperone-binding protein of the immunoglobulin H chain (BiP, additionally known as GRP78). BiP maintains the ER's permeability barrier during protein translocation, assists in protein folding, targets unfolded proteins for degradation, and contributes to the ER Ca^{2+} stores. This activation of apoptosis by CHOP may be responsible for the rod cell death, although the mechanism is not yet known (fig. 3).

Additionally, apoptosis has been implicated in the rod cell loss seen in the *Pde6 β ^{rd1}* mice, but the precise mechanisms that connect the activation of these pathways to the loss of PDE6 β function have yet to be defined [46, 48, 72, 73]. The onset of the rod cell loss in the *Pde6 β ^{rd1}* mutant mice has, however, been associated with elevated cGMP levels, as mentioned earlier. It may also be influenced by the elevated intracellular Ca^{2+} levels that result from the continually open CNG channels arising from high cGMP levels. Thus, cGMP/ Ca^{2+} second messengers may play a role in the activation of cell death, presumably by causing abnormal signaling within rod cells and between the rods and cones.

RP patients with a deficiency in PDE6 have rod photoreceptor cell loss that is a direct consequence of the rod-specific function of PDE6 during the phototransduction cascade. Cone loss, on the other hand, is due to secondary, non-cell-autonomous effects. The pathophysiology is unproved but may involve decreased levels of survival factors produced by healthy rods and/or increased levels of toxic factors produced by diseased rods. These are likely scenarios since rod cells make up 97% of the photoreceptors with cones being only 3% of the cells. Scientists and clinicians have begun searching for therapeutic agents that will be effective in slowing the photoreceptor cell death and/or curing the causative genetic defect.

As a result, the current pathophysiological mechanism of retinal degeneration is still under investigation. However, the mechanisms of cell death after loss of function of PDE6 may be generalizable to loss of function of different key proteins involved in the phototransduction cascade. Furthermore, rod cell death followed by secondary cone cell apoptosis and inner retina remodeling can be found in various common retinal degenerative diseases besides RP, such as Leber congenital amaurosis and AMD.

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Fig. 1. Histological section of the retina. Hematoxylin and eosin-stained section of a C57BL/6J wild-type mouse retina depicting the various cell layers. GCL = Ganglion cell layer; IPL = inner plexiform layer; INL = inner nuclear layer; OPL = outer plexiform layer; ONL = outer nuclear layer.

Fig. 2.

Phototransduction cascade. **a** Key genes involved in the phototransduction cascade during the dark, where cGMP is maintained within the rod photoreceptor cell and the CNG channels are open to allow an influx of sodium ions and Ca²⁺. **b** Key genes involved in the phototransduction cascade during light stimulation, where the cascade is activated leading to the breakdown of cGMP and the closure of the CNG channels.

Fig. 3. UPR pathway. The three integral membrane proteins that are activated to initiate the UPR pathway: PERK, ATF6 and IRE1. PERK = Pancreatic ER eIF2 α kinase; K = RNA-binding domain; ATF6 = activating transcription factor 6; bZIP = basic leucine zipper domain; R = regulatory domain.