Review: The history and role of naturally occurring mouse models with Pde6b mutations

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Mouse models are useful tools for developing potential therapies for human inherited retinal diseases, such as retinitis pigmentosa (RP), since more strains are being identified with the same mutant genes and phenotypes as humans with corresponding retinal degenerative diseases. Mutations in the beta subunit of the human rod phosphodiesterase (PDE6B) gene are a common cause of autosomal recessive RP (arRP). This article focuses on two well-established naturally occurring mouse models of arRP caused by spontaneous mutations in Pde6b, their discovery, phenotype, mechanism of degeneration, strengths and limitations, and therapeutic approaches to restore vision and delay disease progression. Viral vector, especially adeno-associated viral vector (AAV) -mediated gene replacement therapy, pharmacological treatment, cell-based therapy and other approaches that extend the therapeutic window of treatment, is a potentially promising strategy for improving photoreceptor function and significantly slowing the process of retinal degeneration.

Retinitis pigmentosa (RP) is a family of inherited diseases with clinical and genetic heterogeneity causing retinal dysfunction and eventual photoreceptor cell death [1-3]. RP can be either autosomal dominant, autosomal recessive, or X-linked [4-6]. Mutations in the phosphodiesterase 6B, cyclic guanosine monophosphate-specific, rod, beta (PDE6B) gene encoding the beta subunit of phosphodiesterase have been linked to autosomal recessive RP (arRP) in humans [7-9]. Retinitis pigmentosa resulting from mutations in the PDE6B gene is one of the earliest onset and most aggressive forms of this disease, accounting for up to 5% of arRP [7,9].

Rod PDE is a membrane-associated protein composed of two distinct catalytic subunits (PDE6A, PDE6B) of approximately 99 kDa, and two identical gamma inhibitory subunits (approximately 10 kDa). Both catalytic subunits contain two high-affinity non-catalytic cyclic guanosine monophosphate (cGMP) binding sites and a C-terminal half representing the catalytic domain [10,11]. PDE is an essential part of the phototransduction cascade, playing a role in hydrolyzing the cGMP second messenger and resulting in channel closure in response to light [12].

Mutations in Pde6b result in a nonfunctional PDE and an accumulation of cGMP [13-15]. In cells with the defective PDE6B enzyme, increased levels of cGMP lead to photoreceptor cell death [3,15-17]. In this review, we describe the role of two well-characterized, naturally occurring mouse lines with defects in Pde6b as ocular models for the human disease [18,19], particularly focusing on various therapeutic studies to compare the potential for treating this form of RP.

Naturally occurring mouse models of Pde6b retinitis pigmentosa: The rd1 (rodless) mouse model of arRP is characterized by severe, early onset, rapid retinal degeneration caused by mutations in Pde6b [13,20]. The mutant Pde6b gene in rd1 mice, mapped on chromosome 5 [21], contains a murine leukemia provirus insertion in intron 1 and a point mutation, which introduces a stop codon in exon 7 (Figure 1) [22,23]. A rodless retina (gene symbol, r, rd, rd1) was discovered in mice by Keeler and was first reported in 1924 as an autosomal recessive mutation leading to the absence of visual cells (rods), including the outer nuclear layer [24,25]. This animal-related work continued in the United States and Europe over the next decade, but Keeler’s stock was lost by the end of World War II [26]. In 1951, Bruckner reported a similar retinal abnormality that he first recognized in wild mice with ophthalmoscopy [27]. Using PCR analysis of DNA from archival retinal sections, Pitler et al. demonstrated that this line of rd mice contained a homozygous nonsense point mutation in exon 7 (codon 347) and intronic polymorphisms in the Pde6b gene identical to those in the rodless strain initially discovered by Keeler [28]. Histological analysis showed that the outer segments (OSs) and inner segments (ISs) of the photoreceptors were never well developed in rd mice [13,29]. At P10, the OS discs showed signs of disruption, the chromatin was fragmented, and TUNEL-positive photoreceptor cells increased with a rapid loss of rods by P14. In all regions of the eye, rapid rod degeneration preceded...
cone degeneration. Only about 2% of the rods remained in the posterior region at P17, and none by P36. In contrast, at least 75% of the cone nuclei remained at P17 in rd mice. As the retinal degeneration developed, the outer nuclear layer (ONL) became rapidly thinner but left a single row of cone perikarya at 18 months of age [29,30].

In addition to the established role as an animal model for recessive RP, the rd1 mouse, as a source of rodless retinas, has been used for cDNA microarray gene expression studies to elucidate the molecular pathways underlying photoreceptor cell death [31], and to determine the endogenous source of mRNA transcripts for proteins whose cellular localization is unknown [32,33]. Comparative studies use real-time quantitative reverse transcription (RT)–PCR using cDNA samples from rd1 retinas devoid of photoreceptor cells and wild-type controls have confirmed either the rod-specific expression of genes or whether a particular transcript originates mainly from the inner retina [32,33]. Rodless mice have also been used to study circadian entrainment, pupillary constriction, and intrinsically sensitive melanopsin-positive ganglion cells [34-37].

The rd10 mouse, first described by Chang et al. in 2002, carries a missense mutation (R560C) in exon 13 of the Pde6b gene, and represents another useful natural model of recessive retinal degeneration [20,38]. In contrast to rd1, in which PDE6B protein expression and activity are undetectable, rd10 mice are characterized by a relatively slower onset of retinal degeneration, with decreased PDE activity. PDE6B protein can be detected early in rd10 mouse retinas (P10) with western blotting and immunostaining, although the level of expression was significantly reduced compared to that of age-matched wild-type controls [38]. In rd1 mice, peak photoreceptor cell death occurs before full development of the retinal structures, whereas most cells in rd10 mouse retinas have terminally matured before degeneration occurs [38,39]. Histological examination reveals progressive ONL degeneration in rd10 mice, starting from the central retina at P16 and spreading to the peripheral retina by P20. Rapid degeneration occurs between P18 and P25, and by P60, most of the photoreceptors disappear, although the thickness of the INL and the ganglion cell layer is not yet affected. Sclerotic retinal vessels appear at 4 weeks of age in rd10 mice, and retinal degeneration can be easily distinguished at 2 months of age with fundoscopy [38,39]. Dark-rearing rd10 mice further slows the retinal degeneration rate by as much as 3 months [38,40].

The maximal electroretinogram (ERG) response in cyclic light-reared rd10 occurs at 3 weeks and is undetectable at 2 months of age [38]. In contrast, rd1 mice do not generate a scotopic ERG response at any age due to a complete lack of functional PDE6B. Furthermore, aggressive rd1 retinal degeneration cannot be delayed by rearing the mice in darkness (Figure 2) [38]. The residual activity of PDE6b in rd10 retinas may prevent a toxic increase in cGMP early in the mouse’s life, thus delaying the onset of photoreceptor cell death, and extending the window for therapeutic interventions. Many missense pathogenic human mutations in PDE6B leading to autosomal recessive retinitis pigmentosa are located within the catalytic domain [9], potentially resulting in partial loss of function and reduced PDE6B enzymatic activity, as seen in rd10. Thus, the rd10 represents a better mouse model than rd1 for developing strategies for treating human patients with recessive RP.

Figure 1. Schematic representation of the mouse PDE6B gene and protein, and the localization of spontaneous mutations in animal models. The rd1 mouse contains a murine leukemia provirus insertion in intron 1 and a point mutation, which introduces a stop codon in exon 7. The rd10 mouse carries a missense mutation (R560C) in exon 13. Two canine models, the rcd1 Irish setter and the Sloughi dog, contain a nonsense amber mutation at codon 807 (W807ter) and an 8 bp insertion after codon 816, respectively. The PDE6B protein contains two high-affinity non-catalytic cGMP binding sites (GAF domains) and a catalytic domain in which the majority of human mutations are located. Reprinted from Vision Research, vol. 49(22), Baehr W. and Frederick J.M., Naturally occurring animal models with outer retina phenotypes, 2636–2652, 2009, with permission from Elsevier.
Therapeutic approaches:

Pharmacological treatment—Several pharmacology-based treatments were developed to temporarily delay the photoreceptor degeneration in mouse models caused by PDE6B deficiency [41]. In 1999, one study showed that D-cis-diltiazem, a calcium-channel blocker that also acts on light-sensitive cGMP-gated channels, rescued photoreceptors and preserved visual function in the rd1 mouse [42]. The dihydropyridine, diltiazem, is a competitive antagonist of L-type calcium channels. The D-cis stereoisomer is the active compound in several commonly used prescription drugs. Since rd1 rods begin to degenerate due to apoptosis caused by Ca\(^{2+}\) overload around P10 [43,44], intraperitoneal injections of D-cis-diltiazem was applied at P9. Retinal whole mounts and sections were labeled with an antibody against rhodopsin and showed more positive staining in treated mice, which were supported by a measurable scotopic ERG b-wave (approximately 20 μV) at P36. Additionally, the diltiazem-treated cohort at P36 had approximately 18,600 surviving rods, a two- to threefold increase compared to 7,500 rods in the untreated eyes; a modest protective effect on cone survival was also observed [42]. Other laboratories also concluded that D-cis-diltiazem could partially protect photoreceptor cells for the short term in the rd1 mouse [45]. These studies provided evidence that suitable pharmacological approaches to vision protection could be obtained through managing Ca\(^{2+}\) overload [46,47]. Controversially, Pawlyk et al. concluded that there was no significant difference between treated and untreated rd1 mice following D-cis-diltiazem treatment [48].

LaVail et al. have shown that intravitreal delivery of survival factors, such as brain-derived neurotrophic factor (BDNF), neurotrophin-3, neurotrophin-4, and ciliary neurotrophic factor (CNTF), in several animal models of retinal degeneration, including rd1, can slow the progression of photoreceptor cell death [49]. CNTF, especially, has been shown to increase photoreceptor survival as a neuroprotective factor [50,51]. A study by Cayouette et al. used an adenoviral vector to deliver CNTF intravitreally to rd1 mouse eyes, resulting in increased photoreceptor survival [52]. Treatment with CNTF in combination with BDNF was also shown to rescue photoreceptors in cultured rd1 retinal explants [53]. The therapeutic efficacy of encapsulated CNTF-secreting cell therapy was demonstrated in the rcd1 canine model of RP [51,54].

Frasson et al. attempted to treat rd1 degeneration by delivering glial cell line–derived neurotrophic factor (GDNF) into the rd1 eyes at 13 and 17 days of age via sub-retinal delivery [55]. GDNF provided histological and functional neuroprotective benefits on rod photoreceptors in the rd1 mouse, although the effects were partial and temporary. Ohnaka et al. have also shown that GDNF can temporarily slow photoreceptor cell loss in rd10 mice [56].

Systemic administration of recombinant erythropoietin (Epo), an oxygen-regulated hormone, has also been shown to have protective effects on photoreceptor cells in either light-induced or certain inherited forms of retinal degeneration [57,58]. Rex et al. have shown that Epo protein expression following systemic adeno-associated viral (AAV)–mediated...
gene delivery resulted in improved retinal morphology in the rds/peripherin (Prph2), but not the rd10 mouse model of retinal degeneration [58]. Another study indicated that activation of bone marrow–derived microglia following systemic injections with Epo and granulocyte colony-stimulating factor slowed retinal degeneration in rd10 mice, as indicated by increased outer nuclear layer thickness at P30 [59].

An indirect way of extending photoreceptor survival without pharmacological treatment is environmental enrichment, which may lead to an increase in the endogenous levels of potentially beneficial trophic factors. Barone et al. have shown that prolonged exposure of rd10 mice to an enriched environment from birth had protective effects on retinal function and morphology, leading to a decrease in their retinal degeneration rate and increased expression of retinal CNTF mRNA [60].

Tauroursodeoxycholic acid (TUDCA), the active antioxidant component in bear bile, has been used in traditional Chinese medicine for thousands of years. TUDCA acts via a phosphatidylinositol 3-kinase (PI3K)-dependent signaling pathway to block neuronal death triggered by amyloid-β peptide [61]. In 2006, Boatright et al. showed that more photoreceptors survived and better photoreceptor morphology was maintained, and the dark-adapted ERG a- and b-waves and amplitudes were significantly greater by P18 when TUDCA was injected subcutaneously in the nape of P6 rd10 mice [62]. TUDCA-treated retinas showed almost no TUNEL signal and much less immunoreactivity for activated caspase-3. These findings clearly indicate that TUDCA injections suppress apoptosis in rd10 mice. Similar studies also found that the overall morphology of the photoreceptor cells was better preserved in the TUDCA-treated rd10 eyes at P30 and P38 [63-65].

Komeima et al. have demonstrated the beneficial effects of antioxidants in slowing the photoreceptor degeneration process in rd1 and rd10 mice [66,67]. Systemic delivery of combined antioxidants, including alpha-tocopherol, ascorbic acid, and alpha-lipoic acid, reduced cone cell death in both models. The rd10 mouse displayed substantial therapeutic effects, such as better preservation of cone function and retinal morphology, due to the later onset of photoreceptor cell death in this model compared to rd1. Another study showed that a combination of antioxidants, such as lutein, zeaxanthin, and alpha lipoic acid, slowed rd1 rod photoreceptor degeneration following early administration [68].

**Cell-based therapy and optogenetic approaches:** Stem cell-based therapy and optogenetic approaches have the potential to restore visual function for late stages of retinal degeneration, by either focusing on replacing the lost photoreceptor cells or by rendering the remaining bipolar and ganglion cells photosensitive [69-72]. Adult bone marrow contains a population of hematopoietic stem cells (HSCs) that can be divided into lineage positive (Lin+) and lineage negative (Lin-) cells. The Lin- subpopulation contains various progenitor cells capable of becoming vascular endothelial cells [73]. These endothelial progenitor cells can mobilize in response to various signaling molecules and target sites of angiogenesis in ischemic peripheral vasculature. Otani et al. reported that intravitreal injection of adult bone marrow–derived Lin- HSCs at P6 could completely prevent retinal vascular degeneration in the rd1 mouse [74]. Furthermore, this vascular rescue correlated with neuronal rescue: The INL remained nearly normal, and the ONL was partially preserved, with the rescued cells predominantly cones [74]. This study suggests that the rescue effect of Lin- HSCs can last for as long as 6 months if the cells are injected just before the onset of degeneration, but the ERG amplitudes were only 8–10 μV at 2 months after treatment. The ERG amplitudes in the rescued eyes were considerably lower than that of the gene therapy-based rescue studies (see below). Sasahara et al. later showed that endogenous bone marrow–derived microglia played a protective role in vascular and neural degeneration in rd1 and rd10 mice [59].

In addition to stem cells, Barber et al. have shown that photoreceptor transplantation is feasible in several mouse models at different stages of retinal degeneration, including rd1, and the recipient microenvironmen111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111
glutamate receptor to restore light responsiveness to the retinal ganglion cells of adult rd1 mice [82].

Gene replacement therapy: Due to the early and rapid rate of photoreceptor cell loss in the rd1 mouse, providing effective gene therapy in a timely manner to rescue visual function in this animal model have proved difficult. In the early 1990s, Bennett et al. found that the photoreceptors of the rd1 mouse could be partially rescued with in vivo gene therapy, thus supporting the feasibility of treating inherited retinal degeneration with somatic gene therapy [83]. Bennett et al. conducted an experiment with sub-retinal injection of a recombinant replication-defective adenovirus that contained murine cDNA for β-PDE, Ad-CMV-βPDE. Sub-retinal injection of Ad-CMV-βPDE resulted in β-PDE transcripts, increased PDE activity, and delayed photoreceptor cell death by 6 weeks. However, this early generation of adenoviral vectors had limitations, including short-term expression of the transduced gene due to immune response against the adenoviral vector. Additionally, the rescue effect was not long lasting. Subsequently, other researchers switched to an encapsidated adenovirus minichromosome (EAM), which showed relatively longer transgene expression [84,85]. EAM-mediated delivery of the β-subunit of cGMP phosphodiesterase cDNA to rd1 mice showed prolonged β-PDE expression and rescue of rod photoreceptor cells [84]. RT–PCR analysis from the injected retina indicated that transgene products were present for up to 18 weeks post-injection. Examination of outer nuclear thickness showed significant differences until 12 weeks post-injection [84].

Jomary et al. also evaluated the efficacy of a recombinant AAV vector for delivering and expressing the β-PDE gene in the retinas of rd1 mice [86]. Following intraocular injection of AAV2-β-PDE, increased retinal expression of immunoreactive PDE protein was observed, including expression within photoreceptor cell bodies. Compared with the age-matched untreated controls, the treated eyes showed only a modest delay in photoreceptor degeneration. A major limitation of that study was the use of a low-titer traditional AAV2 vector in an animal model of rapid retinal degeneration. Since then, major progress has been made in vector purification methods and capsid engineering, resulting in high-titer AAVs of different serotypes with faster onset of expression and improved transduction efficiency [87-89]. Sub-retinal delivery of these optimized vectors in the rd10 mouse with a slower degeneration rate, as described below, has led to significant recovery of retinal function and morphological preservation by providing therapeutic levels of transgene expression before the photoreceptor cell loss.

Researchers also showed that lentiviral vectors based on human immunodeficiency virus (HIV) type 1 can achieve stable and efficient gene transfer into retinal cells [90,91]. Takahashi et al. tried the HIV1-based lentiviral vector to rescue retinal degeneration in rd1 mice [92]. Lentiviral vector containing Pde6b under the control of the cytomegalovirus promoter or rhodopsin promoter was injected into the subretinal space of rd1 eyes between P2 and P5. One to three rows of photoreceptor nuclei were observed in the eyes for at least 24 weeks post-injection. In summary, sub-retinal injection of adenoviral, adeno-associated viral, or lentiviral vectors encoding the Pde6b gene in neonatal rd1 mice resulted in partial preservation of photoreceptor structure although retinal function with ERG was never well restored.

The rd10 mouse is more amenable to successful gene replacement therapy than rd1, since the rd10 mouse displays a later onset and slower retinal degeneration process, thus providing a longer therapeutic window for intervention [38]. In 2008, Pang et al. reported a successful gene replacement therapy using AAV5 to rescue rd10 mice [93]. Since light exposure may speed up retinal degeneration, dark-reared P14 rd10 mice were injected sub-retinally with an AAV5-5-smCBA-PDEβ vector under dim light, resulting in prolonged photoreceptor survival and improved ERG and vision-guided performance for at least 3 weeks after sub-retinal injection. However, the therapeutic effects faded 6 weeks after treatment. Since photoreceptor degeneration starts around P16 in rd10 mice, and the AAV5-PDE6b vector takes at least 1 week to express enough functional protein following sub-retinal injection, treatment earlier than P9 in the rd10 mouse could lead to even more rescue. In reality, it is difficult to detach a significant fraction of the mouse retina following trans-cornea sub-retinal injection with minimal injection-related damage before the mouse eyes open around P14 [94]. Although trans-sclera sub-retinal injection can be used for neonatal mouse treatment, the injection transduces only a small part of the retina with extensive sub-retinal injection-related complications [95,96]. For example, in rd10 mice, AAV5-mediated rescue following P14 treatment [93] is more robust than that following P2 treatment [97] with a similar AAV5 vector when both cases are evaluated at P35. An optimal stable rescue could be related to the extent of retinal coverage by the vector and might be offset by injection-related damage to the neonatal mouse eye [98]. Yao et al. have shown that an AAV5-mediated delivery of the X-linked inhibitor of apoptosis at P4 can significantly slow photoreceptor degeneration in combination with gene-replacement therapy and may extend the window of treatment [99].
A tyrosine-capsid mutant AAV8 (Y733F) vector capable of transducing most of the photoreceptors within several days following sub-retinal injection represents a useful tool for treatment in animal models with early onset of retinal degeneration [100]. Consequently, a more significant rescue was achieved by using this capsid mutant serotype, compared to an AAV5 vector containing the same Pde6b gene [98]. Sub-retinal injection of the tyrosine-capsid mutant AAV8 (Y733F)-smCBA-PDE6b in the same dark-reared P14 rd10 mice led to restored retinal function and improved visual behavioral performance. Additionally, more than half of the photoreceptors were preserved for at least 6 months, as determined with ERG, optomotor behavioral tests, spectral domain optical coherence tomography (SD-OCT), and histology. Secondary retinal degeneration and remodeling in older rd10 mice were also prevented in rd10 eyes treated at P14, which lasted for at least 6 months [98]. Although the cause of the protective effect of dark-rearing on the progression of retinal degeneration is not completely understood, the effect may have implications for treating human patients with PDE-based mutations [40]. The long-term rescue effect in rd10 mice using the potent capsid mutant AAV8 vector provides a promising approach for gene therapy for patients with RP and paves the way for potential clinical trials in the future.

Mouse models of recessive RP have demonstrated that gene replacement therapy holds great promise for treating monogenic disorders [101-104]. Although both naturally occurring mouse models presented here mimic certain features of the clinical phenotype of recessive RP found in human patients with Pde6b mutations, the therapeutic findings may not fully extend to the human disease [105]. Mouse eyes are not similar to those of humans, due to the small size, low cone to rod ratio, and absence of a macula. The successful restoration of retinal function in mouse models of arRP, such as rd10, can be attributed in part to the ability to transduce the entire retina following a single sub-retinal delivery of a small volume of vector. We noticed the rescue effect fades within several months if the treated retinal area is less than 50% [98]. The widespread distribution of the vector following intraocular delivery in mouse models allows the majority of mutant photoreceptors to receive the missing functional gene. In contrast, transduction in human patients is restricted to a small area (10%–15%) of the retina following a single sub-retinal injection, and the remaining untreated photoreceptors may exert a negative effect on the neighboring cells during the course of degeneration. Consequently, one major goal of current gene therapy studies is to develop highly efficient and penetrating AAV vectors that can transduce photoreceptor cells over the entire retina following intravitreal delivery [100,106], and avoid the damage associated with sub-retinal surgical procedures, especially around the sensitive foveal region [107]. As demonstrated by experiments in animal models of recessive RP, gene therapy is most effective when treatment is initiated early, before the onset of photoreceptor cell death [108,109]. A recent study of human patients with RPE65-associated Leber congenital amaurosis (LCA2) has shown that although gene therapy led to substantial visual improvement, retinal degeneration continued to progress in the treated and untreated regions of the retina [110]. To better evaluate the treatment options for human patients with arRP caused by mutations in PDE6B, more studies are needed to explore the effects of therapeutic interventions in larger animal models at various stages of photoreceptor degeneration. Two naturally occurring canine models with recessive mutations in Pde6b have previously been described, the rcd1 Irish setter, which contains a nonsense amber mutation at codon 807 (W807ter) causing a truncation of the PDE β-subunit, and the Sloughi dog, caused by an 8 bp insertion after codon 816 [111,112]. A recent study identified a three base pair deletion in exon 21 in ccred1 dogs, leading to partial loss of PDE6B function and a relatively slower rate in photoreceptor cell loss, similar to human patients [113]. These larger animal models more closely mimic the human eye and can provide more translational knowledge of disease progression and therapeutic interventions for arRP caused by Pde6b mutations.

Conclusions: This review focused on the pathogenesis of natural mouse models of recessive RP caused by Pde6b mutations, and the current available therapeutic options. Although some of the treatments discussed lead to partial protection of the morphology and function of photoreceptors, gene therapy is the only currently available technology that halts apoptosis and maintains long-term functional rescue, when treatment is provided before photoreceptor cell death is initiated. The rd10 mouse model of recessive RP, with later onset of retinal degeneration than rd1
reagents, could become an important strategy for treating autosomal recessive RP in the future.

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