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Retinitis pigmentosa

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CONTENTS

Abstract

Retinitis pigmentosa refers to a group of hereditary diseases that cause vision loss due to progressive degeneration of photoreceptor cells, ultimately leading to blindness. Retinitis pigmentosa is a genetically heterogeneous disease associated with mutations in over 50 identified genes. Currently, there is no cure for the condition, but recent research efforts have unveiled new therapeutic approaches. This article highlights some of the most relevant findings from basic and clinical research.

Introduction

Retinitis pigmentosa is not a single medical entity, but rather a term that designates three hereditary forms of photoreceptor degeneration, with an estimated prevalence ranging from of 1 per 3,000 to 1 per 7,000 cases (1). Retinitis pigmentosa can be inherited in an autosomal dominant (ADRP) or autosomal recessive (ARRP) form or as an X-linked trait. Most cases initiate with loss of rod photoreceptor cells, which typically causes night blindness (nyctalopia), progressing to cone degeneration at later disease stages and affecting diurnal vision. Fundus examination reveals bone spicule-shaped pigment deposits initially in the peripheral retina, pallor of the optic disk and attenuated retinal vessels. The electroretinogram (ERG) usually shows decreased α- and β-wave amplitudes (2). This clinical picture progresses into the mid and late stages, in which symptoms worsen, with total loss of peripheral vision and progressive loss of the central visual field in daylight, eventually leading to blindness. Data from a centralized Irish registry of blind people reported retinitis pigmentosa as the third cause of registration (7%) behind age-related macular degeneration (25%) and glaucoma (12%) (3).

Retinitis pigmentosa is usually classified as syndromic or nonsyndromic. In around 20-30% of cases it can be associated with rare nonocular disorders such as Usher's or Bardet-Biedl syndrome. In Usher's syndrome, retinitis pigmentosa generally presents with either profound (type I) or mild to moderate hearing loss (type II), associated or not with vestibular ataxia. Late-onset hearing loss can occur (type III).

In Bardet-Biedl syndrome, retinitis pigmentosa is concomitant with obesity, cognitive deficits, polydactyly, hypogenitalism and renal disease. Other syndromes that have been linked to retinitis pigmentosa include Senior-Loken and Alport's syndromes, dysmorphic syndromes (Cohen, Jeune and Cockayne's syndromes) and some rare metabolic and neurological diseases (2, 4).

Pathogenesis

Photoreceptor physiology

Loss of vision in retinitis pigmentosa is due to the degeneration of the two photoreceptor types in the retina: rods and cones. Rods and cones form the outer nuclear layer of the retina (Fig. 1), which in retinitis pigmentosa is markedly diminished. The inner nuclear layer that contains amacrine and horizontal cells and the ganglion cell layer are initially spared, but may also degenerate at later disease stages. Rods are responsible for vision under dim illumination conditions (*i.e.*, achromatic or night vision), whereas cones mediate daylight and color vision. Visual transduction requires visual pigments contained in photoreceptor cells. Rhodopsin, the light-sensitive visual pigment in rods, is formed by a covalent complex of opsin, a large membrane protein, and a light-sensitive vitamin A derivative called retinal. Upon light absorption, a change in the retinal configuration from the *cis* to the *trans* form induces conformational changes that activate the rhodopsin molecule. The active form of rhodopsin (metarhodopsin II) binds to the G-protein transducin, which further activates cGMP phosphodiesterase. A reduction in the intracellular cGMP concentration closes cGMP-activated cation channels in the retina, followed by a decrease in membrane potential (hyperpolarization), which is the trigger for further activation of bipolar and

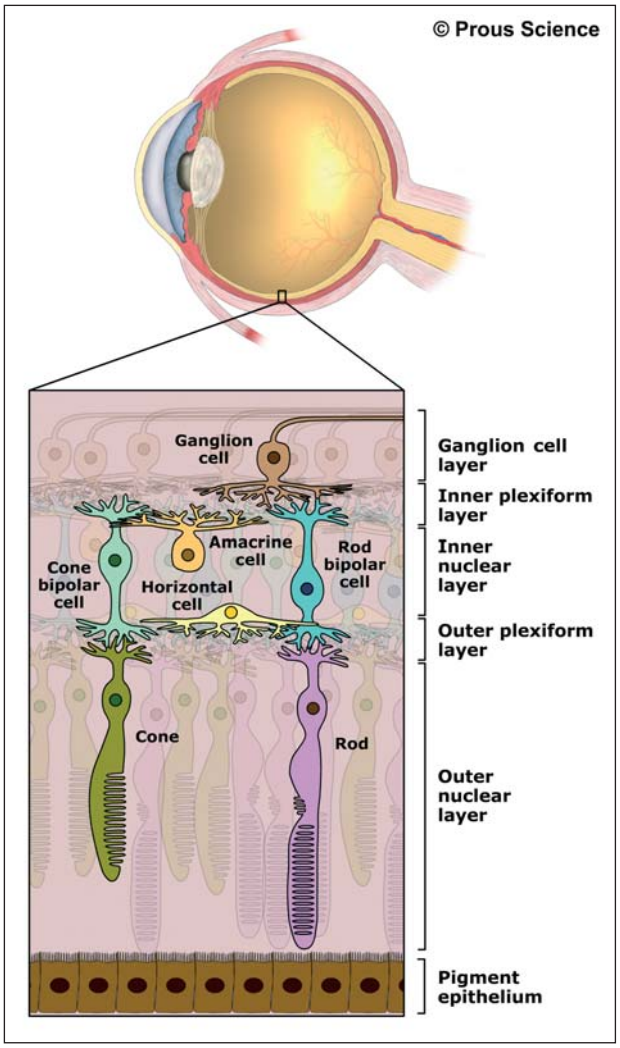

Fig. 1. The human retina is approximately 0.5 mm thick and formed of three layers of nerve cell bodies and two layers of synapses. Rods and cones form the outer nuclear layer of the retina, whereas the inner nuclear layer contains cell bodies of amacrine and horizontal interneurons, and the ganglion cell layer is formed by cell bodies of ganglion cells. Rods and cones absorb light and convert it to electrochemical signals. Synaptic contacts take place at the outer plexiform layer, where connections between rods and cones and bipolar and horizontal cells occur. In turn, bipolar cells transport visual information from the outer plexiform layer to the inner plexiform layer via synaptic contacts with amacrine, horizontal and ganglion cells. These latter cells then convey the message to central vision structures through the optic nerve.

ganglion cells and transduction of the visual impulse to the brain visual centers via the optic nerve (5).

Photoreceptor apoptosis in retinitis pigmentosa

Extensive research has shed light on apoptotic pathways involved in photoreceptor degeneration in retinitis pigmentosa. Activation of endoplasmic reticulum (ER) stress pathways that involve calpain-dependent processes has been recognized as the most prominent form of apoptosis in models of both ADRP and ARRP. Conventional initiator and effector caspase signaling appears not to be involved in mediating photoreceptor cell death in retinitis pigmentosa models (6), although it cannot be completely ruled out (7-9).

Calpains are calcium-dependent cysteine proteases that are associated in the ER with calpastatin, an endogenous calpain inhibitor, which, upon an increase in intracellular calcium, dissociates from the calpain heterodimer, resulting in calpain activation. Intracellular calcium overload and persistent ER stress are two well-characterized triggers of calpain-dependent cell death (10). ER stress occurs due to the accumulation of misfolded proteins in the ER, which activate the unfolded protein response (UPR), which in turn reduces the protein translation rate and increases misfolded protein degradation. However, the UPR cannot cope with prolonged ER stress and apoptosis is then activated. One of the signals that initiates the apoptotic response is calcium release from the ER, which is also the trigger for calpain activation (11).

Rd1 is a mouse model of ARRP caused by a mutated form of the *PDE6B* gene encoding the β subunit of the rod photoreceptor cGMP phosphodiesterase (PDE). Lack of PDE activity causes cGMP accumulation and calcium entry through cGMP-gated channels, which in *rd1* mice has been shown to correlate with increased intracellular calcium levels (12), calpain activation (12, 13) and translocation of apoptosis-inducing factor (AIF) and caspase-12 from the mitochondria and ER, respectively, to the nucleus in apoptotic rods. Moreover, intravitreous injection of calpain inhibitors completely suppressed rod apoptosis in *rd1* mice (14). Accumulation of mutant rhodopsin protein in the ER has also been shown in models of ADRP in *Drosophila* (15, 16) and is associated with rod photoreceptor apoptosis via activation of the stress-specific mitogen-activated protein kinases (MAPKs) p38 and JNK (15).

The therapeutic use of calpain inhibitors has been explored by Senju researchers, who reported that a single oral dose of SNJ-1945 (200 mg/kg) prevented photoreceptor cell death in a mouse model of *N*-methyl-*N*-nitrosourea-induced retinal degeneration (17).

Genetics

To date, mutations in 53 genes have been associated with nonsyndromic retinitis pigmentosa. Mutations in the rhodopsin (*RHO*) gene account for about 25% of autosomal dominant retinitis pigmentosa cases, with a proline substitution at position 23 by histidine (Pro23His) being the most common. As for autosomal recessive retinitis pigmentosa, about 10% of cases in this disease type are caused by mutations in the *USH2A* gene, whereas mutations in the *RPGR* (retinitis pigmentosa GTPase regulator) gene represent approximately 70% of cases of X-linked retinitis pigmentosa (1).

Retinitis pigmentosa-associated genes are functionally diverse and can encode ocular or widely expressed proteins. Thus, mutations in genes involved in visual transduction, such as rhodopsin, or encoding photoreceptor structural proteins, like retinal outer segment membrane protein 1 (*ROM1*), will interfere with photoreceptor function and precipitate photoreceptor death. As for widely expressed genes, only retinal isoforms have been found to cause photoreceptor degeneration, as has been described for IMP dehydrogenase type 1 (*IMPDH1*), a housekeeping gene controlling guanine synthesis (18). In general, no precise correlation exists between disease phenotype and the type of mutation, although in some cases the mutated gene can predict disease severity (1). An extensive listing of genes associated with retinitis pigmentosa has been published elsewhere (19).

Treatment

The gradual loss of photoreceptor cells is the hallmark of retinitis pigmentosa and therapies are aimed at preventing or delaying photoreceptor cell death. Photoreceptor neuroprotection, replacement of mutant genes or defective protein repair are some of the targeted strategies under investigation for the treatment of retinitis pigmentosa. Additionally, nonpharmacological approaches such as retinal implants or photoreceptor transplantation are alternative options that may benefit patients with profound loss of photoreceptor cells in late stages of the disease.

Current options

1. Antioxidants

The therapeutic use of vitamins A and E in retinitis pigmentosa was examined more than a decade ago by Berson *et al.* (20, 21), who observed that a daily supplement of 1500 IU of vitamin A delayed disease progression as measured by ERG recordings. Retinitis pigmentosa patients in groups A and A+E demonstrated a significantly lower rate of vision loss than those receiving trace doses of vitamin A. Moreover, a daily dose of 400 IU of vitamin E was associated with a faster decline in vision and the authors suggested that high-dose vitamin E supplements should be avoided. Further safety assessments of long-term daily vitamin A supplements in retinitis pigmentosa reported 8% and 18% increases in serum retinol concentrations after 5 and 12 years of therapy, respectively, with no retinol values exceeding the upper normal limits. No vitamin A-associated liver toxicity was observed (18-54 years) (22). Further studies investigating the effects of vitamin A supplementation in retinitis pigmentosa are ongoing (23-25).

Lutein, a naturally occurring carotenoid with antioxidant properties, has demonstrated rather limited therapeutic utility in retinitis pigmentosa, as well as in macular degeneration. A randomized, double-blind, placebo-controlled clinical study investigated the effects of lutein supplementation in 34 patients with retinitis pigmentosa and found that the visual field was preserved when assuming a 6-week delay in the onset of lutein effect (26, 27). However, no significant changes in visual acuity were associated with lutein treatment.

2. Omega-3 fatty acids

Omega-3 fatty acid supplementation has been suggested to be of potential therapeutic utility in slowing the progression of retinitis pigmentosa. The biological rationale for this assumption relies on the fact that elevated levels of omega-3 fatty acids, and in particular docosahexaenoic acid (DHA), form part of the rhodopsin lipid scaffolding in photoreceptor outer segments. Maturation of retinal function, visual acuity and visual transduction are some of the functions attributed to DHA in photoreceptors (28).

However, results gathered from recent clinical studies are inconclusive. A trend towards improvement in retinitis pigmentosa symptoms with DHA supplementation or an omega-3 fatty acid-rich diet over 2 years, in addition to vitamin A treatment, has been described (29). However, this research group failed to demonstrate the same visual benefit over a 4-year period (30). Another study evaluating DHA supplementation in X-linked retinitis pigmentosa found no significant overall changes in loss of functional cones in ERG analysis, but it preserved rod ERG function in patients younger than 12 years (31, 32).

A systematic review analysis performed by Canadian researchers concluded that, although there is a trend for improvement with omega-3 fatty acid supplementation, further clinical investigation is required (33). Currently, a 4-year study evaluating the safety and efficacy of a high-dose nutritional DHA supplement in patients with X-linked retinitis pigmentosa is being conducted by Martek Biosciences (34).

Future therapies

Experimental therapies for the treatment of retinitis pigmentosa undergoing development are depicted in Table I.

1. Ciliary neurotrophic factor

Ciliary neurotrophic factor (CNTF) is a member of the interleukin-6 (IL-6) family of cytokines known to be involved in photoreceptor cell neuroprotection in animal models of retinal disease, likely due to activation of CREB neuronal survival pathways (35). Using an encapsulated cell-based delivery system, researchers at Neurotech Pharmaceuticals have shown protective effects for CNTF in rats carrying the rhodopsin mutation S334ter and in dogs with rode-cone dysplasia (*rcd1*) caused by mutations in the *PDE6B* gene (36). This system, also called NT-501, consists of human retinal pigment epithelial cells genetically modified to produce CNTF and encapsulated in a semipermeable membrane, which allows diffusion of CNTF and nutrients and protects from the host immune response. NT-501 has been designed to ensure sustained CNTF release (> 100 ng/10^6 cells/24 h) in the vit-

Table I: Investigational therapies under development for retinitis pigmentosa (from Prous Science Integrity®).

Drug	Description	Source	Phase
ECT-CNTF/NT-501	Encapsulated cell-based delivery of ciliary neurotrophic factor (CNTF)	Neurotech Pharmaceuticals	II/III
FOV-2501	Intravitreal formulation of rod-derived cone viability factor (RdCVF)	Fovea Pharmaceuticals	Preclinical
AVT-2	Lentivirus-based delivery of RdCVF	Advanced Vision Therapies	Preclinical
GT-015	Short hairpin RNA (shRNA)-based therapy to suppress and replace mutant rhodopsin	Genable Technologies	Preclinical
GT-025	shRNA-based therapy to suppress and replace mutant rhodopsin	Genable Technologies	Preclinical

reous for long periods of time. Severe photoreceptor degeneration was observed in untreated eyes in both animal models, whereas CNTF treatment protected photoreceptor cells in a dose-dependent manner.

The good tolerability of NT-501 in preclinical studies encouraged further investigation in humans. A nonrandomized, open-label, dose-escalating phase I clinical trial evaluated the safety of NT-501 in patients with severe retinal photoreceptor degeneration due to retinitis pigmentosa (37). In this study, intraocular implants were surgically placed in the vitreous cavity of 10 patients for a period of 6 months. Promising safety results were obtained, with no systemic or ocular complications reported, with the exception of a single shallow choroidal detachment that resolved after topical corticosteroid treatment and did not require implant removal. Although the study was not designed to test clinical efficacy, visual acuity could be followed in 3 patients, who showed increases of 10-15 letters over baseline, corresponding to a 2-3-line improvement in standard Snellen acuity charts. Implants removed at study completion contained viable cells that still produced CNTF at therapeutic levels. Furthermore, cell loss was minimal and no histological signs of inflammation were present.

Recently, enrollment has begun for two randomized, double-blind, sham-controlled, dose-ranging phase II/III trials of NT-501 implants in patients with early- and late-stage retinitis pigmentosa, respectively (38, 39). However, experimental data from a canine model of X-linked retinitis pigmentosa have shown that CNTF therapy may not be effective in all types of inherited retinal degeneration (40).

2. Gene therapy

Due to the genetic heterogeneity of this disease, gene therapy approaches to treat retinitis pigmentosa remain a challenge. However, several gene-based therapies are currently being investigated (see Table I). Preserving cone photoreceptor function is another therapeutic strategy in retinitis pigmentosa, as cones are essential for fine daylight vision. In 2004, researchers at Fovea Pharmaceuticals identified the rod-derived cone viability factor (RdCVF), a protein expressed in the photoreceptor layer of the retina that has shown neuroprotective activity on cones *in vitro* and on cones of *rd1* mice upon subretinal space injection (41). FOV-2501 is an intravitreal formulation of RdCVF that is currently being developed at Fovea Pharmaceuticals and that is scheduled to enter the clinic in 2009 (42).

Similarly, Advanced Vision Therapies is developing AVT-2, a lentiviral vector carrying RdCVF designed as a treatment for retinitis pigmentosa (43). This novel virus-based gene transfer system possesses adequate gene-transducing ability, but a reduced risk of recombination due to elimination of sequence homologies between the transfer and the packaging vector, hence minimizing the potential safety issues associated with therapeutic viral vectors (44).

In addition, Genable Technologies is focusing on therapies for rhodopsin-linked ADRP involving suppression and replacement of the mutated *RHO* gene. This technology consists of delivering a short hairpin RNA (shRNA) that will target and suppress mutated *RHO,* via a recombinant adeno-associated virus (AAV). This vector also encodes a *RHO*-complementary DNA (cDNA) with a modified sequence in the target RNA interference site to avoid suppression. This technology has been tested via subretinal injection to transgenic mice expressing mutant *RHO* (Pro23His) (45). Previous studies evaluated the efficacy of suppression and replacement strategies individually. Different synthesized shRNA constructs markedly suppress *RHO* gene expression when electroporated in mouse retinal explant tissue. Moreover, modified replacement *RHO* cDNAs have been shown to rescue retinal pathology in *RHO* knockout mice (46).

3. Antibiotics

The tetracycline antibiotic minocycline has shown neuroprotective activity in several animal models of neurodegenerative diseases, such as Alzheimer's disease (47) and multiple sclerosis (48, 49). The mechanism by which minocycline exerts neuroprotection has been attributed to inhibition of poly(ADP-ribose) polymerase type 1 (PARP1) activity (K_i = 13.8 nM against recombinant PARP1) (50). Recent findings have demonstrated excessive PARP activity in the retina of *rd1* mice, which was associated with increased photoreceptor cell death markers and nuclear translocation of AIF (51). Suppression of PARP activity by a highly specific inhibitor, namely PJ-34, decreased the number of dying *rd1* photoreceptors in

short-term cultures *in vitro* and increased photoreceptor survival in long-term treatment cultures. However, studies in *rd1* mice treated with minocycline have only reported a delay in the onset of photoreceptor cell death, but not complete prevention (52). A possible explanation for these results may be the presence of different signaling pathways that lead to photoreceptor cell death in retinitis pigmentosa models, suggesting the need for multitargeted therapeutic approaches for the treatment of this disease.

Aminoglycoside antibiotics are known to induce translational readthrough of premature stop codons by interfering with the proofreading property of the ribosome, hence allowing translation of full-length proteins. Recent findings have demonstrated the utility of gentamicin in delaying photoreceptor degeneration in the SS334er rat model of retinitis pigmentosa, in which animals express a truncated rhodopsin lacking the last 15 amino acids, caused by a premature stop codon. Mutated rhodopsin exhibits prolonged activation in response to light and impaired trafficking of the opsin part to the photoreceptor's outer segment, which leads to rod cell death. In this study, subcutaneous gentamicin (50 μg/g) slowed the degeneration rate of photoreceptors, achieving control levels after approximately 2 months of treatment (53).

4. Electrical stimulation implants

Electrical stimulation of the remaining intact photoreceptor retinal layer has been suggested as a means to improve vision in retinitis pigmentosa patients with extremely reduced visual acuity. Researchers at Optobionics have investigated the feasibility of using an artificial silicon microchip containing about 5,000 microphotodiodes that incorporate a stimulating electrode sensitive to external incident light in patients with retinitis pigmentosa (54). Results from this pilot study indicated significant promise, as subjective visual improvements in brightness, contrast, shape or visual field were reported, with no related safety concerns.

Researchers at Intelligent Medical Implants have designed a retinal implant system consisting of three main components: an integrated microchip that electrically stimulates the retina, a visual interface (glasses equipped with a camera that presents real-time images to the subject) and a pocket processor (55, 56). Results of a pilot study conducted in 4 patients with retinitis pigmentosa and a visual acuity of light localization or less, demonstrated the feasibility of this chronic implant system, which was well tolerated for up to approximately 9 months (follow-up period) (57). An extension of this pilot study is currently ongoing (58).

A similar device has been developed by Second Sight®. The Argus™ II Retinal Stimulation System consists of a camera and a transmitter mounted in eyeglasses that transmit the image and convert it to an electrical signal that, via an implanted receiver, will reach an array of 60 electrodes attached to the retina, which will generate electrical pulses to stimulate the retina. Preliminary results from a pilot study evaluating a first-generation 16-electrode implant (Argus™ 16 Retinal Stimulation System) prosthesis showed that patients perceived light and could perform spatial and motion tasks (59, 60). The Argus™ II Retinal Stimulation System is being investigated in feasibility studies in blind subjects with severe to profound retinitis pigmentosa (61).

5. Transplantation

Transplantation of human photoreceptors is another proposed strategy to fight vision loss in retinitis pigmentosa. Transplanted photoreceptors may act as a source of trophic factors required for cone viability, or could reconstitute the disrupted retinal neural network. Although the safety and feasibility of allogeneic transplantation of human photoreceptors (either of adult or fetal origin) has been proven (62, 63), clinical benefit is inconclusive. However, vision improvement was reported in an isolated case of a 64-year-old woman whose visual acuity improved from 20/800 to 20/160 at 1 year post-transplantation of an intact sheet of fetal neural retina and retinal pigment epithelium. No signs of clinical rejection were observed at 1 year after the transplant (64). This research group is testing the safety of this procedure in an open clinical trial in patients with decreased central visual acuity of 20/200 or worse (65).

Conclusions

Retinitis pigmentosa is a serious, potentially blinding disease that affects a significant number of people worldwide. There is currently no cure for retinitis pigmentosa and traditional therapies have achieved only partial success in controlling disease progression. However, therapies undergoing clinical development, such as CNTF retinal delivery, provide new hope for the treatment of retinitis pigmentosa, as first-in-human trials have been particularly encouraging. Although still preliminary, gene-based therapies have also provided promising results in preclinical studies. Moreover, retinal stimulation devices and the transplantation of photoreceptor cells is focusing on improving vision and maintaining independence in more severely visually impaired patients. Growing knowledge of causative genes and biochemical pathways affected in retinitis pigmentosa will be key to identifying new drug targets that will lead to viable therapies for the treatment of this disease.

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