International Journal of Research in Medical Sciences
Sariningsih S. Int J Res Med Sci. 2024 May;12(5):1776-1783
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012

DOI: https://dx.doi.org/10.18203/2320-6012.ijrms20241274

Review Article

The pathophysiology and therapeutic approaches in retinitis pigmentosa

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Received: 05 March 2024
Revised: 17 April 2024
Accepted: 18 April 2024

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ABSTRACT

Retinitis Pigmentosa is a prevalent hereditary retinopathy that involves the gradual deterioration of vision cells and the disturbance of retinal pigment epithelium. The typical triad of retinitis pigmentosa is the pigmentation of the bone spicules, blood vessel constriction, and pallor of the optic nerve. The variety of clinical presentations is nyctalopia, tunnel vision, loss of colour discrimination, and in a later stage, complete loss of visual acuity. The immense genetic mutation accounts for the pathogenesis of RP. This diverse mutation makes treatment exceptionally challenging for RP. Until now, there is no specific therapy recommended for RP. Gene therapy is possibly the best option for RP, but further clinical trials are needed to provide customized therapy for each patient. Various therapeutic trials use pharmacologic agents such as neurotrophic, anti-apoptotic, antioxidant, anti-inflammatory, and anti-VEGF also use to postpone the progressivities of RP.

Keywords: Retinitis pigmentosa pathophysiology, Retinitis pigmentosa therapy, Retinitis pigmentosa epidemiology

INTRODUCTION

Retinitis Pigmentosa (RP) is a genetic retinal disease described by progressive degeneration of the visual cells and disruption of retinal pigment epithelium (RPE). 2.5 billion people suffer from Retinitis Pigmentosa, making RP the most common genetical retinopathy.[1-3] There are substantial clinical presentations in RP. Nyctalopia or night blindness during early adolescence is usually the first symptom, along with progressive cell death. Further loss of rods in the peripheral retina, where these cells predominate, decreases the visual field (tunnel vision).[1,3] Progressive severity of RP results in complete vision loss over time. As the result of disease progression, other abnormalities may also develop, including impairment of accurate colour differentiation and eventual loss of visual acuity. Some light perception will be preserved in most patients, even with severe RP, as the macula carries on its function.

Photopsia (perceived flashes of light) is arguably the most disturbing late effect of RP due to sensory deprivation. The progression of photopsia may result in the establishment of visual hallucinations.[1] Biochemical dysfunction results from genetic mutations responsible for retinitis pigmentosa, which explicitly affects rod photoreceptors (rods and cones) in the retina and, specifically, in the RPE cells. These faults may be associated with multiple pathways of injury. The immense genetic diversity, with more than 3000 mutations, in 54 genes and 61 loci, became the hallmark of RP.[3,4] This diverse mutation makes treatment exceptionally challenging for RP. Even though various therapeutic trials have been done using numerous pharmacologic agents, most are not targeted the pivotal pathophysiology of RP, and the efficacy has not been proven.[1,2] In this article, we review the pathophysiology and future therapeutic strategies of RP. This review may help understand the updated possible treatment for RP.

Epidemiology

An estimated 2.5 million people are suffering from retinitis pigmentosa worldwide. Nevertheless, the prevalence is underestimated in some populations. Most cases of RP are categorized into the nonsyndromic category. The prevalence of RP in males is higher than in females due to males' X-linked form being expressed more frequently. Syndromic RP's prevalence is less common, with Usher syndrome estimates from 1.8 to 6.2 cases per 100,000 persons. The genetic type of RP influences the average age of symptom onset. Individuals with autosomal recessive will develop symptoms in early adolescence, but those affected with autosomal dominant RP most likely will develop symptoms later into their 20s. More than 75% of people with RP will have symptoms and seek medical assessment and diagnosis before the age of 30.[1,5]

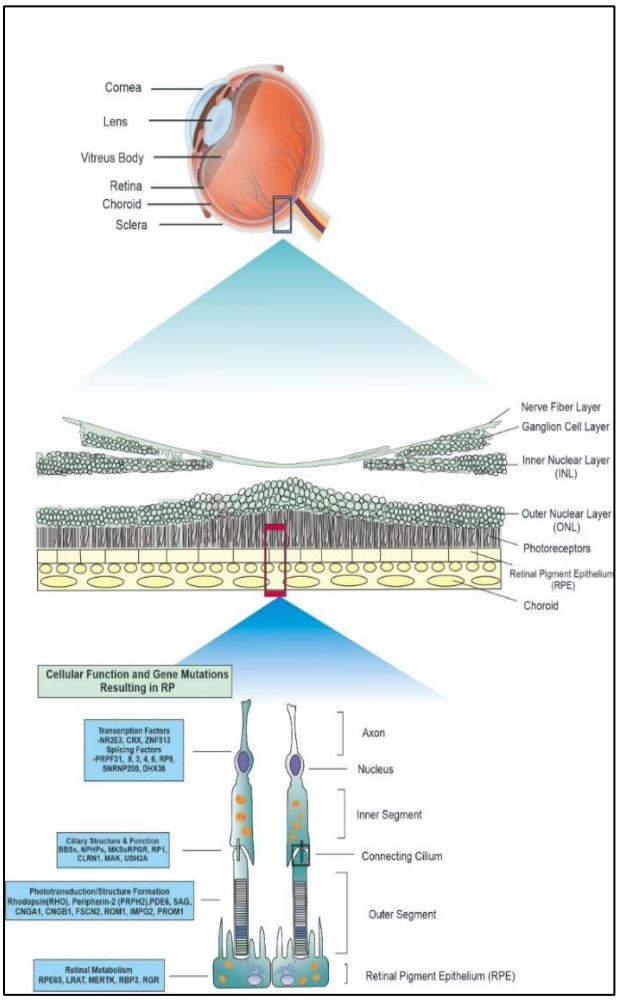

Figure 1: Overview of the structure of the human retinal layer and the location of proteins known or thought to be translated by RP-associated genes in photoreceptor rods or RPE cells. Outer retinal cells photoreceptors (cones and rods) and RPE are the primary target cells for treating retinitis pigmentosa.[2]

PATHOPHYSIOLOGY

As stated before, various genetically directed mechanisms contributed to the progress of retinitis pigmentosa. Apoptosis is a physiological program of cell death, which genetic mutations can trigger. Apoptosis can also be triggered by communication between photoreceptor cells.[1,6] Thus, the presence of rod cell death can eventually spread to cone receptors as well. The presence of excessive light exposure can also exacerbate the phototoxic mechanism. These mechanisms include mutations in retinol metabolism and accelerated oxygen consumption in the environment, increasing the degeneration of both rods and cones of photoreceptors. The function of cilia is essential for causing cell susceptibility. The presence of stress on the endoplasmic reticulum induces the release of free radicals, coupled with the stimulation of retinal hypoperfusion conditions and vascular endothelial cell damage.[1]

The typical triad of retinitis pigmentosa is the presence of pigmentation of the bone spicules, constriction of blood vessels, and pallor of the optic nerve. Melanin pigment deposits, caused by retinal pigment epithelial cells shed and migrating to perivascular locations in the retina, are named after the characteristic star shape of the bone spicules. The precise origin of this migration is not completely comprehended, nor is the constriction of the retinal arteries. However, one hypothesis proposes that it arises from diminished metabolic requirements caused by the demise of numerous photoreceptors. Changes in the appearance of the optic disc may be due to the formation of glial cells that cover the disc and increase reflectivity, producing a "wax pale" appearance.[7]

Molecular genetics of RP

The genetic basis and mutations that cause RP are complex and diverse. Genetic overlap between RP and other types of hereditary retinal dystrophic disorders suggests similar underlying mechanisms and common genetic pathways, despite differences in clinical features.[8,9] A total of 70 genes have been associated with RP. RP inheritance consists of autosomal dominant (15-25%), autosomal recessive (5-20%), X-linked (5-15%), and unknown patterns (40-50%). The central genes causing RP are Rho, RPRF, PRPH2, RP1, IMPDH1, and PRPF8 for adRP; USH2A, ABCA4, PDE6A, PDE6B, and RPE65 for arRP; RPGR and RP1 for xlRP. Most genes cause RP to take up a small part of the entire gene. The RHO gene accounts for about 20-30% of adRP cases, and the USH2A gene accounts for about 10-15% of arRP. The RPGR and RP1 genes are responsible for the majority of xlRP cases. The presence of mutations in RHO, USH2A, and RPGR is found in approximately 30% of cases of RP.[10,11]

Genes and disease mechanisms of RP

Mutant proteins' diverse biological functions in RP also account for disease heterogeneity. The main biological mechanisms related to RP gene activity are phototransduction cascade, retinal transcription factor-associated pathways, RNA splicing machinery, retinal metabolism, retinal cell structure, and ciliary structure and function. (Figure 1).[2]

Autosomal dominant

Twenty-two gene mutations have been identified that cause autosomal dominant RP. However, only a few genes (RHO, PRPF31, PRPH2, and RP1) explain the occurrence of most cases of autosomal dominant RP. The RHO gene encodes Rhodopsin, G Protein-Coupled Receptors (GPCRs), which can be photoexcited in the outer rod segment disk membrane. GPCRs are composed of a protein (Rhodopsin) and a chromophore (11-cis-retinal). When light energy is taken in by the retina, Rhodopsin triggers the activation of the GTP-binding protein, transducin, which then initiates the phototransduction cascade. Then transducin is activated and combined with GTP, forming the transducin-GTP complex, which further activates cyclic guanosine monophosphate (cGMP) phosphodiesterase (PDE) can hydrolyze cGMP. This process causes the closure of cation channels and a sequential change in the rate of neurotransmitter release from photoreceptor cells and modulates the process of visual phototransduction. It is known that the leading cause of RP is the mutation of the RHO gene (20-30% autosomal dominant RP, 10% of all RP cases). There are 204 mutations divided into six classes of mutation types (Figure 2).[2] Class I mutations have a proper folding process, but an error occurs when carried to the outer segment; class II mutations are misfolded and retained in the endoplasmic reticulum (ER); Class III mutations disrupt the process of endocytosis. Class IV mutations do not impact the folding process, but they do affect important post-translational modifications such as glycosylation, disulfide bond formation, acetylation, palmitoylation, phosphorylation, and ubiquitination, which are crucial for the function of Rhodopsin and the structure of the outer retinal segment. In class V mutations, folding errors are not detected, but there is an increase in transducin activation. Class VI mutations result in properly folded Rhodopsin, but the opsin is activated without the presence of the chromophore. Lastly, there are numerous mutations that cannot be classified or have not been extensively studied.[12,13]

Autosomal recessive

Although more than 30 genes have been identified in the occurrence of autosomal recessive RP, most genes account for only a tiny percentage of autosomal recessive RP. However, some genes, RPE65, PDE6A, PDE6B, and RP25, have a higher percentage, up to 2-5% of cases. An essential enzyme for restoring visual pigment in cones and rods in the retinal pigment epithelium is the Retina Pigment Epithelium 65 kDa protein (RPE65).

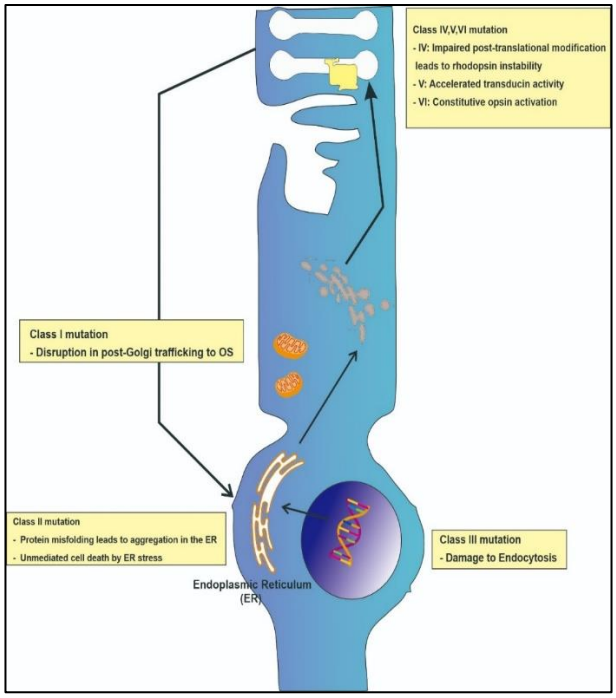

Figure 2: Six classifications of Rhodopsin gene mutations. Sites of mutations are L328, T342, Q344, V345, A346, P347 (Class I); T17, P23, G51, T58, V87, G89, G106, C110, L125, A164, C167, P171, Y178, E181, G182, C187, G188, D190, H211, C222, P267, S270, K296 (Class II); R135 (Class III); T4 (Class IV); M44, V137 (Class V); G90, T94, A292 (Class VI); N15, Q28, L40, F45, L46, P53, G109, G114, S127, L131, Y136, C140, E150, P170, G174, P180, Q184, S186, T193, M207, V209, P215, M216, F220, E249, G284, T289, S297, E341 (Unclassified).[2]

More than 60 distinct mutations in RPE65 have been identified and are responsible for approximately 2% of cases of recessive RP and 6% of cases of Leber's congenital amaurosis (LCA).[2] Several genes are closely related to the phototransduction cascade of the genes that cause RP. PDE6 (Rod cGMP-specific 3′,5′-cyclic phosphodies-terase) is a protein complex consisting of two subunits encoded by PDE6A, PDE6B, and PDE6G and located on the outer segment of the photoreceptor. The PDE6 complex regulates the opening and closing of cGMP-gate cation channels in rods and cones, which is vital in transmitting and amplifying visual signals. The importance of the PDE6 complex for photoreceptor function and maintenance, mutations in PDE6A and PDE6B, causes arRP by incorporating calcium into rod cells and inducing apoptosis. Furthermore, photoisomerization of 11-cis to all-trans-retinal is the initial step of the phototransduction cascade process to convert light stimuli into electrical signals, and the reconversion of non-photoactive all-trans-retinal to

photoactive 11-cis-retinal is essential for its recombination with opsin to form a visual pigment. RPE65 catalyzes the conversion of all-trans to 11-cis-retinal that occurs in RPE.[14,15]

X-linked

X-linked RP (XLRP) has the typical characteristics of early onset and severe clinical manifestations, and it is known that there are 10-15% of RP patients diagnosed with XLRP. RPGR (retinitis pigmentosa GTPase regulator) and RP2 (retinitis pigmentosa 2) are the two primary genes that cause XLRP. Mutations in the RPGR gene were found in 70% of XLRP patients, 25% of male RP patients without a family history, and 11% of all RP patients. The RPGR gene can be identified in various cilia-associated tissues, including photoreceptors connecting cilia, the respiratory epithelium motile cilia, and the human fetal cochlea. Although the molecular function of the RPGR is not clearly understood, it accommodates the processes of disc morphogenesis, intracellular transport of opsin from the inner segment to the outer segment, and transport from the nucleus to the cytoplasm. The RPGR and RP2 genes are present in 80% of cases of XLRP, in contrast to other types of RP, making them strong candidates for genetic therapy.[2,16]

Cone photoreceptor death in RP

Mutations causing RP cause death of rods, but not cones, because the mutated gene is expressed differently in rods and cones (e.g., Rhodopsin), or the mutated gene is indeed expressed in both cells but plays a more critical role in supporting function and rod cell survival. Rod and cone cell dystrophy from multiple gene mutations impairs their function, but it has a different phenotype from RP.[17] Rod cell death due to gene mutation is always followed by cone cell death. One theory is that rod cell death also causes cone cell death. This is due to the activity of dying rod cells releasing toxic substances through gap junctions which are then transmitted to cone cells, and the activity of microglia to clean dead rod cells, but then participate in damaging cone cells or from the elimination of factors necessary for the survival of cone cells. However, most cone cell deaths occur years after all rods are lost, and it is challenging to identify toxins released from dying rods, microglial activity due to rod cell death, or lack of viable survival factors derived from rod cells. In addition, deletion of connexin36, an essential component of gap junctions, does not affect the pattern or timing of cone cell death.[19] However, reduced trophic support from rods and other cells may influence cone cell death, and there is evidence to suggest that such trophic factors do exist. Alternative splicing of Nxnl1 mRNA expressed in rod cells and other retina cells yield two proteins as short-rod-derived cone survival factors (RdCVF-S) and RdCVF-long (RdCVF-L) that aid cone cell survival.[20,21] If the loss of RdCVF-S and RdCVF-L produced by rods were the leading cause of cone cell death in RP, a knockout of Nxnl1 resulted in significant loss of cones as was the case in RP, but the Nxnl1-/- model mice only showed a 17% reduction in cone cell density and a 20% reduction in Outer Nuclear Layer (ONL) thickness indicating a 20% reduction in rod cells. Thus, the trophic effects of RdCVF are not specific to cones and are considered non-essential for cone cell survival, but their absence increases the risk of exposure to oxidative stress (including hyperoxia) and metabolic stress due to lack of glucose uptake. Thus, loss of RdCVF is not the leading cause of cone cell death in RP but may affect overall cone cell survival.[17] As noted above, loss of RdCVF increases the susceptibility of cone cells to oxidative stress. Changes in retinal gene expression assessed at various stages of degeneration using microarrays showed upregulation of 230 genes in the early process of cone cell degeneration and about one-third of the described genes involved in cellular metabolism. The insulin/ mTOR pathway that regulates aspects of cellular metabolism is the highest number of regulated genes. Activating the insulin/mTOR pathway in cone cells enhances the expression of genes involved in glucose uptake and utilization and enhances cone survival in 2 RP models. This suggests that metabolic stress contributes to cone cell death, but it is unclear how the mechanism works.[17]

THERAPEUTIC APPROACHES FOR RP

Gene therapy

Until now, there is no specific therapy recommended for RP. There has been rapid progress in understanding the pathophysiology, especially the genetic and molecular determinants underlying RP. The restoration of visual acuity in Leber Congenital Amaurosis (LCA) patients due to mutations in the gene encoding the retinal pigment epithelial protein (RPE65) was necessary for photoreceptor physiological activity and is the first example of gene therapy in the CNS. Complete recovery of visual acuity was found in one eye of 50 patients who had a single subretinal injection of adeno-associated viral vectors (AAV) at the first appointment. AAV transduced outer retinal cells and RPE and delivered copies of the normal RPE65 gene.[22] A study showing the results of a clinical trial in six male patients with choroideremia, which is a severe X-linked disease that causes visual acuity loss through progressive atrophy and degeneration of the choroid, RPE, and outer retina due to mutations in the CHM gene, which encodes a protein (REP1), and this protein plays a significant role in cellular trafficking.[23] A gene augmentation study reported consistent data, which found improvements in rod and cone cell function in treated patients. These data support further studies of gene therapy for other retinal diseases.[24] Clinical trials have been registered for gene therapy of two types of retinal degeneration caused by recessive mutations. The first is RP38, caused by mutation of MERTK, a human receptor tyrosine kinase that plays a role in cytoskeletal remodeling to engulf outer segment debris during phagocytosis by RPE; and Usher 1B syndrome, caused by mutations in the MYO7A gene, which encodes an

unusual myosin. Both mutations cause progressive visual impairment, resulting in severe visual acuity loss. Additional studies are needed for X-linked RP due to mutations in the Retinitis Pigmentosa GTP-ase Regulator (RPGR), a protein that is localized to the outer segment of rod cell photoreceptors and plays a vital role in rod cell survival; and mutation of the beta subunit of rod cell-specific phosphodiesterase (PDE6B) in autosomal recessive RP.[3] Further clinical trials are needed for gene therapy tailored to each patient-specific mutation that must confront the disease's enormous genetic heterogeneity and the procedure's relatively high costs. Therefore, soon it seems unlikely that gene therapy will turn out to become a widespread treatment for RP.[3]

Pharmacological approaches

There is no significant evidence regarding the role of pharmacological therapy in preventing the progression of RP or restoring vision. Most pharmacological agents provide neuroprotection in the hope of slowing the progression of the disease to maintain visual function for the rest of their lives.[25] So that pharmacological therapy does not modify the underlying cause of RP but only provides supportive and conservative therapy. There are additional treatments for complications secondary to RP, such as cystoid macular oedema and cataracts. Although the effectiveness of these therapies has not been proven and provides only minor visual improvements that are not significant or are expected to slow the progression of RP, these are an option for patients without alternative treatments.[2]

Neuroprotection

In experimental animals with multiple retinal dystrophy, photoreceptor cell death is caused by apoptosis, a physiological mechanism that programs cell death. Neuroprotective agents, including anti-apoptotic neurotropic drugs and antioxidants, have been extensively studied to delay rod cell death and protect against secondary cone cell loss in RP.[2]

Neurotrophic agents

A neurotrophic factor is a small, endogenously secreted protein with a short half-life.[25] Generally, neurotrophic factors aid in the maturation process, maintain the viability and growth of developing neurons, and aid in the maintenance of mature neurons.[26] RPE and Müller cells are the eye's main sources of neurotrophic molecules.[27,28] Test Clinical and animal model studies have shown that several neurotrophic and growth factors protect photoreceptor cells.[26] Some of the most studied neuroprotectors are the Ciliary Neurotrophic Factor (CNTF), Brain Derived Neurotrophic Factor (BDNF), Fibroblast Growth Factor (FGF), and Glial cell Derived Neurotrophic Factor (GDNF).[29] Acid and alkaline Fibroblast Growth Factor (aFGF and bFGF), Leukemia Inhibitory Factor (LIF), Pigment Epithelium Derived Factor (PEDF), cardiotrophin 1, Nerve Growth Factor (NGF), Rods Derived Cone Viability Factor (RdCVF) and Lens Epithelium Derived Growth Factor (LEDGF) are also neurotrophic which have been tested for their effectiveness.[29,30]

The primary mechanism underlying the CNTF-mediated neuroprotective effect is thought to be due to the upregulation of proteolysis inhibitors, which can prevent cellular/extracellular matrix degradation and complement activation processes in several neurodegenerative diseases, including RP.[31] These factors are thought to inhibit the adverse effects of the enzyme in the phototransduction cascade that can impair photoreceptor function. The lack of clinical trials of these agents, due to their short half-lives, makes the need for repeated doses a major limitation to treatment. However, a clinical study demonstrated that intravitreal CNTF implantation (NT-501) in the early and late stages of RP results in a reversible short-term loss of total visual field sensitivity, and no improvement in visual acuity field sensitivity or improvement of retinal structures were found. In the long term (60-96 months).[2]

Anti-apoptotic agents

Apoptosis is an important mechanism of photoreceptor degeneration in RP, so pharmacological therapy that manipulates cell death pathways using anti-apoptotic agents can reduce photoreceptor degeneration in RP. Studies using tauroursodeoxycholic acid (TUDCA), Rasagiline, Norgestrel, and Myriocin in RP animal models, demonstrated a slowdown in different apoptotic pathways photoreceptors be preserved.[3,27,32,33] TUDCA has been reported to exert a protective effect on retinal degeneration. TUDCA also helps to promote photoreceptor outer segment phagocytosis through activation of Mer tyrosine kinase (MerTK). (34) Drack et al. conducted a study using different models for RP, and subcutaneous injection of this substance demonstrated neuroprotective activity in two different models, including Bardet-Biedl syndrome, the most common form of RP syndrome.[32] Caspase-mediated inhibition of apoptosis is associated with the protective activity.[35] Rasagiline is a monoamine oxidase inhibitor with neuroprotective activity by inhibiting pro-apoptotic pathways and inducing anti-apoptotic proteins. Studies using a mouse model of Prph2/rds, have shown that this substance can exert significant anti-apoptotic activity on photoreceptor cells at low doses through a caspase-dependent pathway.[33] Norgestrel is a synthetic derivative of progesterone that has been used in several oral contraceptives and demonstrated a neuroprotective effect in animal models with RP. The neuroprotective effects may be produced by regulating bFGF and kinases and LIF, critical factors for retinal cell survival under stress conditions.[20] Research on progesterone was shown to be neuroprotective in retinal cells and to delay disease progression in an animal model of RP.[36]

Antioxidant agents

The retina is the most sensitive reactive oxygen species (ROS) tissue. Photoreceptors are one of the largest oxygen consumers in the central nervous system due to the high concentration of mitochondria in the ellipsoid. Photoreceptors become highly susceptible to oxidative stress due to the large surface area of the disc membrane enriched with polyunsaturated fats and metabolic rate. Thus, the role of antioxidant agents is essential in the retina, especially in photoreceptors.[27] Vitamin A, DHA (Docosahexaenoic acid), and lutein are the only antioxidant agents studied through large-scale, long-term randomized clinical trials. However, there are no precise clinical trial results, so the exact clinical importance should be concluded with caution.[2] Recent studies using curcumin supplementation have been conducted. Polyvinyl is a yellow pigment found in the rhizome of the Curcuma plant and is known for its anti-inflammatory and antioxidant activity. The antioxidant effect was seen in retinal cell morphology in RP model mice and pigs.[37] Wolfberry, an antioxidant substance obtained from Lycium barbarum extract known in Chinese medicine, has shown anti-apoptotic, anti-inflammatory, and antioxidant activities in animal models with RP.[38] A study using animal models of RP treated with a mixture of antioxidants (zeaxanthin, lutein, alpha-lipoic acid) dissolved in olive oil and glutathione and Lycium barbarum extract showed reduced cell death. N-acetylcysteine, a glutathione precursor, has also been shown to exert neuroprotective activity in animal models of RP.[2]

Anti-inflammatory agents

Inflammatory processes and immune responses in the pathogenesis of RP have not been studied in depth. There is some evidence to suggest a possible role for inflammatory conditions in the pathogenesis of RP. The finding of retinal autoantibodies in the systemic circulation in patients with RP and rodent models, the discovery of immune cells in the vitreous cavity, and the finding of elevated levels of pro-inflammatory cytokines and chemokines in the aqueous humor and vitreous in RP patients. systemic response to the ocular inflammatory reaction, thus targeting the inflammatory response as a potential treatment of RP. Studies using fluocinolone acetonide in mouse models for RP show an increased disease phenotype.[2] Steroids have anti-inflammatory and anti-angiogenic effects, inhibiting blood vessel leakage. Several case reports of RP treated with intravitreal corticosteroids such as triamcinolone and dexamethasone (Ozurdex) implants have shown a dramatic short-term improvement in visual acuity.[40] A retrospective multicenter study, including 45 eyes with CME due to RP treated with dexamethasone intravitreal implants, showed improvement in visual acuity for up to 4 months in about half of the eyes.[41] There are limitations to using intravitreal steroids, where the duration of effectiveness is short, so frequent repetition is required. The side effects of repeated injection procedures are cataract formation and glaucoma induction.[40,41]

Anti-VEGF agents

Bevacizumab, ranibizumab, and aflibercept are intravitreal anti-VEGF agents. Clinical studies and case reports using all three agents have shown effective responses in RP patients with CME, such as decreased macular thickness and increased visual acuity.[40,42] Intravitreal use of anti-VEGF agents is superior to intravitreal steroid use because of fewer side effects. Therefore, it is safer for long-term treatment of RP patients with CME, but larger randomized clinical trials are needed to assess efficacy.[2]

CONCLUSION

The genetic basis and mutations that cause RP are complex and diverse, with 70 genes associated with RP inheritance. Gene therapy has been proposed for RP, but further clinical trials are needed to tailor it to each patient-specific mutation. Pharmacological approaches provide neuroprotection in the hope of slowing the progression of the disease to maintain visual function for the rest of their lives. Neurotrophic agents, such as CNTF, BDNF, FGF, and GDNF, have been shown to reduce photoreceptor degeneration in RP. Antioxidant agents, such as Vitamin A, DHA, and lutein, have shown effective responses in RP patients with CME. This paper presents an overview of the advancements in RPE-related scientific research, particularly in the areas of physiology and therapeutic interventions for RPE. By comprehending the physiology and therapeutic possibilities of the RPE, it is anticipated that there will be further advancements in research, leading to the emergence of novel therapeutic alternatives for physicians.

ACKNOWLEDGEMENTS

Author is thankful to Faculty of Medicine, University of Brawijaya, for the support.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: Sariningsih S. The pathophysiology and therapeutic approaches in retinitis pigmentosa. Int J Res Med Sci 2024;12:1776-83.