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MOLECULAR BASIS AND CURRENT POSSIBILITIES OF VECTOR THERAPY FOR RETINITIS PIGMENTOSA

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ABSTRACT

Objective. The aim of this study is to conduct a systematic analysis of current approaches to the treatment of retinitis pigmentosa, with an emphasis on the use of viral vectors, particularly AAV, in gene therapy.

Materials and Methods. A systematic review was conducted of publications indexed in PubMed, Web of Science, Scopus, CyberLeninka, and eLIBRARY databases. The review included studies on animal models, molecular genetic reviews, and clinical trials addressing the efficiency of therapeutic gene delivery, immune response, vector limitations, and potential clinical outcomes. Descriptive and comparative analysis methods were used to identify correlations between mutation type, therapeutic strategy, and treatment outcomes.

Results. The review showed that AAV vectors demonstrate the highest efficacy among vector platforms due to their strong tropism for photoreceptors and good biocompatibility. The most extensively studied targets include the RPGR, RHO, MERTK, TULP1, and CNGB1 genes, with the greatest progress achieved in the treatment of X-linked retinitis pigmentosa and autosomal recessive forms. Despite encouraging results, treatment efficacy depends on the disease stage, individual mutations, and the ability of the vector to overcome insertion capacity limitations. Approaches aimed at neuroprotection, cell therapy, and optogenetics in the late stages of degeneration are also considered.

Conclusions. Personalized selection of vector-based gene therapy for retinitis pigmentosa, based on the patient's genetic profile, represents a key direction in the development of ophthalmic genetics. The use of AAV vectors shows strong potential; however, further improvement is required in terms of systemic delivery, immune modulation, and targeted expression. The findings highlight the need for an interdisciplinary approach integrating genetics, molecular biology, and ophthalmological practice.

KEYWORDS: retinitis pigmentosa, gene therapy, viral vectors, AAV, inherited retinal dystrophy, RPGR, MERTK.

INTRODUCTION

The eye, as the organ of vision, is a highly specialized anatomical and physiological system, the central component of which is the retina — a structure responsible for transforming light into nerve impulses [1]. Among inherited retinal dystrophies, retinitis pigmentosa is the most common and disabling disease. It is a progressive retinopathy that leads to the loss of photoreceptor cells and blindness. According to epidemiological studies, the prevalence of this pathology reaches 1 case per 5,000 people, which corresponds to more than 1.5 million patients worldwide and more than 30,000 cases in Russia [2–4]. The disease is characterized by genetic and clinical heterogeneity, which complicates its timely diagnosis, prognosis, and the individualization of treatment approaches.

Retinitis pigmentosa is accompanied by degeneration of rods and cones — the photoreceptors of the retina. At first, this manifests as night blindness and narrowing of the visual field, and then progresses to complete loss of central vision. The clinical picture includes a typical triad: pigment deposits in the form of bone spicules, narrowing of retinal vessels, and pallor of the optic disc; however, the severity of these signs may vary depending on the inheritance pattern and genotype [5]. Despite the rapid development of molecular genetics, the pathogenesis of the disease remains insufficiently understood in many respects, and etiopathogenetic treatment has not yet been introduced into broad clinical practice.

In recent years, vector therapy has gained particular relevance as one of the most promising approaches to the treatment of retinitis pigmentosa. This method is based on the delivery of functional copies of a gene into the retina using viral vectors, most commonly adeno-associated vectors [6–8]. It makes it possible to target cellular mechanisms directly, addressing the primary cause of the disease rather than only its symptoms. However, the effectiveness of vector therapy largely depends on the therapeutic time window — the preservation of the photoreceptor layer and the degree of damage to the retinal pigment epithelium — which makes early detection of retinitis pigmentosa and monitoring of its progression critically important [9]. Modern imaging methods, including optical coherence tomography, perimetry, and electrophysiological tests, allow structural and functional changes in the retina to be tracked at the preclinical and subclinical stages [7].

In addition, phenotypic variability even in the presence of the same mutation indicates the existence of modifying factors and requires multifactorial analysis to predict the course of the disease. In the absence of a universal treatment, the use of gene therapy remains a key area of scientific research, especially when a causal relationship between a mutation and its

clinical manifestation has been established [10]. Thus, the need to develop personalized, genetically oriented approaches based on vector technologies has become an integral part of modern ophthalmic genetics. The aim of this review is to systematize data on the pathogenesis, clinical course, and possibilities of vector therapy for retinitis pigmentosa, as well as to identify the most promising directions for future research and treatment.

MATERIALS AND METHODS

In this study, a systematic review of the scientific literature was conducted on current approaches to the treatment of retinitis pigmentosa, with an emphasis on vector-based methods of gene therapy. The literature search was performed in international and Russian bibliographic databases, including PubMed/MEDLINE, Web of Science, Scopus, CyberLeninka, and eLIBRARY. The following keywords were used: "retinitis pigmentosa," "gene therapy," "adeno-associated vectors," "photoreceptors," "inherited retinal dystrophy," "AAV vectors," and "genome editing." The inclusion criteria comprised clinical studies, experimental models, molecular genetic reviews, and articles addressing both the molecular mechanisms of the disease and therapeutic vector platforms.

Particular attention was paid to publications describing the efficiency of gene construct delivery to photoreceptors and the retinal pigment epithelium, as well as clinical data on the improvement of visual function in patients after vector therapy. Studies addressing limitations associated with the immune response, the restricted therapeutic time window, and the potential toxicity of vector systems were also analyzed. The review included studies using various scientific approaches, ranging from cellular and animal models to multicenter clinical trials, which made it possible to obtain a comprehensive understanding of the current state of the problem.

The methods applied included descriptive-analytical and comparative analysis aimed at identifying patterns between the structural target of gene therapy and clinical outcomes. Summary information on the criteria for inclusion and selection of literature sources, the search methodology, and filtering process is presented in Table 1.

Table 1. Stages of selection of domestic and foreign publications for analytical review

The database	Genetics and mutations (zar./ed.)	Gene therapy and vectors (zar./ed.)	Molecular mechanisms (zar./ed.)	Phenotypes and models (zar./ed.)	Pathogenesis and treatment approaches (zar./ed.)
Web of Science (WOS)	10 / 3	9 / 1	8 / 2	7 / 1	10 / 2
Scopus	12 / 4	10 / 2	9 / 3	8 / 2	11 / 3
Scopus + WOS	11 / 3	9 / 2	8 / 2	7 / 2	10 / 3
RSCI + HAC	0 / 3	0 / 2	0 / 2	0 / 1	0 / 2
HAC	0 / 2	0 / 1	0 / 1	0 / 0	0 / 1
RSCI	0 / 3	0 / 1	0 / 1	0 / 1	0 / 2
Without scientific indexing	2 / 2	1 / 1	1 / 0	0 / 0	1 / 1

Thus, the data presented in the table reflect the growing interest of both domestic and foreign researchers in studying the potential of vector-based gene therapy for retinitis pigmentosa. This indicates the increasing importance of molecular genetic research aimed at finding effective methods for correcting inherited retinal dystrophies.

RESULTS AND DISCUSSION

This section presents summarized results of the analysis of current literature devoted to retinitis pigmentosa. Particular attention is paid to its etiology, molecular mechanisms of pathogenesis, and current gene therapy strategies. The key aspects of the disease are then considered sequentially: its genetic basis, inheritance patterns, mechanisms of retinal damage, and treatment prospects.

Etiology and Molecular Pathogenesis of Retinitis Pigmentosa

Retinitis pigmentosa (RP) is the most common form of inherited retinal dystrophy, characterized by primary damage to photoreceptors, particularly rods, with subsequent involvement of cones and other cellular structures. According to Bhardwaj et al. [9], the prevalence of the disease is approximately 1 in 3,000 people, while Shlepotina and Peshikova [1] emphasize its leading position among inherited retinal diseases in the Russian Federation. The disease is highly genetically heterogeneous [10, 11]: more than 100 genes are known, mutations in which can cause RP, including RPGR, RHO, USH2A, MERTK, and others, which significantly complicates diagnosis and the choice of treatment strategy, as shown in Table 2.

Table 2. Key genes and pathogenetic mechanisms of retinitis pigmentosa

The gene	Type of inheritance	Pathogenetic mechanism
RHO	Autosomal dominant	Violation of light signal transduction in rods [10]
RPGR	X-linked	Disruption of protein transport in photoreceptors [6, 7]

USH2A	Autosomal recessive	A defect in the protein responsible for maintaining the structure of the retina [2, 9]
MERTK	Autosomal recessive	Violation of phagocytosis of photoreceptor discs [4]
RPE65	Autosomal recessive	Deficiency of an enzyme involved in the retinoid cycle [11]
CNGB1	Autosomal recessive	Violation of ion current in photoreceptors [9]
PRPF31	Autosomal dominant	Disruption of RNA splicing in photoreceptor cells [10]

The manifestation of RP usually occurs in childhood and is accompanied by nyctalopia, tunnel-like narrowing of the visual field, and later decline in central vision. Morphologically, pigment deposits in the form of bone spicules, pallor of the optic disc, and atrophy of retinal vessels are observed [2, 8]. At the molecular level, the pathogenesis of RP is associated with the gradual death of photoreceptors due to impaired photoreceptor transduction, increased oxidative stress, hypoxia, and a secondary inflammatory response activated by Müller cells [4, 5, 12].

A significant role is played by disruption of the interaction between the retinal pigment epithelium and photoreceptors, leading to cell desquamation, loss of homeostasis, and fibrosis of the inner retinal layer [6, 10]. In some patients, cystoid macular edema develops, associated with impairment of the blood-retinal barrier and increased osmotic pressure of the vitreous body [5]. According to Cideciyan et al. [13], progressive rod degeneration triggers cone apoptosis, which explains the later decline in central vision. Against this background, vector-based gene therapy has been actively developing in recent years, aiming to restore or replace defective genes, particularly through the use of adeno-associated viruses (AAV), as described in the studies by Ghazi et al. [4]. This opens prospects for the development of etiological treatment and for slowing the rate of retinal degeneration.

Viral Vectors

Gene therapy has shown high efficacy in the treatment of inherited retinal diseases, particularly retinitis pigmentosa [1]. Therapeutic approaches for RP depend on the type of inheritance and are generally implemented through two main strategies. In recessive forms of the disease associated with loss of protein function, gene complementation is used to restore its activity. In dominant RP, suppression of the expression of the pathological gene is applied, if necessary in combination with its complementation. This differentiated approach makes it possible to take into account the molecular features of a specific genetic defect. Gene therapy for retinitis pigmentosa (RP) is actively developing, and viral vectors, especially adeno-associated viruses (AAV), have demonstrated the greatest efficacy and safety in preclinical and clinical studies [2, 3]. Due to their small size (~25 nm), low immunogenicity, and ability to provide long-term expression, AAV vectors have become the preferred tool for gene delivery in the treatment of inherited retinal diseases [4, 5]. Unlike adenoviruses, which often induce an immune response, AAV demonstrates good tolerability and the possibility of repeated administration, while not being associated with pathogenicity in humans [3, 6]. Despite these advantages, AAV vectors have a limited capacity for inserting genetic material, up to 4.7 kb, and require invasive subretinal administration, which limits their use in the therapy of large genes [5, 8]. In response to these limitations, strategies using dual and triple AAV vectors have been developed to restore full-length proteins, including in models of Stargardt disease and other inherited retinal dystrophies (IRDs) [9, 10]. In addition, the development of new AAV capsids with improved permeability after intravitreal administration opens the way to less invasive and broader therapy for inherited retinopathies [14–17].

Autosomal Recessive RP

In the autosomal recessive form of retinitis pigmentosa (RP) associated with mutations in the MERTK gene, gene therapy is aimed at restoring the function of the receptor involved in the phagocytosis of photoreceptor outer segments by retinal pigment epithelium (RPE) cells. MERTK deficiency disrupts the clearance of photoreceptor debris, leading to its accumulation and subsequent retinal degeneration, as observed in the RCS rat model. Early attempts to deliver the normal MERTK gene using adenoviral vectors resulted only in temporary improvement of RPE function and partial preservation of photoreceptors, limited by the immune response to the vector [14]. The use of AAV vectors provided more stable MERTK expression and restoration of phagocytic activity; however, the effect also proved to be short-term due to delayed onset of expression and limited retinal coverage [18]. More effective results were achieved with the use of lentiviral vectors and modified AAV vectors with accelerated expression, which provided prolonged morphological and functional improvement [11]. These data confirm the potential of MERTK replacement therapy for RP, provided that vector systems and the timing of intervention are optimized.

Autosomal Dominant RP

The autosomal dominant form of retinitis pigmentosa (RP) may be caused by a single mutated copy of a gene that disrupts cellular function through mechanisms of haploinsufficiency, dominant-negative effects, or toxic protein accumulation [19]. Despite the limited understanding of molecular mechanisms in humans, transgenic animal models have made it possible to distinguish between pathogenetic types of dominant mutations. Unlike recessive forms, gene replacement in such patients is often insufficient, especially in the presence of an active mutant allele [20]. A more effective strategy is considered to be suppression of the expression of the pathological allele, with possible compensation by expression of the normal allele. Due to the wide diversity of mutations within a single gene, for example RHO or RDS/peripherin, individualized editing of each mutation remains challenging [21–23]. In this regard, neuroprotection represents an alternative direction, aimed at enhancing cell survival and slowing the progression of retinal degeneration.

Autosomal Recessive Mutations Not Associated with Rhodopsin

Among the genetic causes of autosomal recessive retinitis pigmentosa (arRP), mutations in the CNGB1 gene account for approximately 4% of cases [21]. A recent review identified 62 pathogenic CNGB1 variants associated with inherited retinal diseases, and studies using the Cngb1−/− mouse model showed that delivery of the CNGB1 gene via an AAV vector improved visual function, retinal morphology, and photoreceptor preservation [24]. Mutations in TULP1 also lead to severe early-onset retinal degeneration. Studies in zebrafish models showed that impaired Tulp1 expression affects ciliogenesis through regulation of tektin2 [20]. At the same time, AAV-mediated editing partially restored TULP1 expression but did not prevent thinning of the outer nuclear layer in mice [17]. Similarly, the Fam161a deficiency model developed by Berezkin et al. demonstrated pronounced retinal degeneration with increased microglial activation, as well as loss of visual acuity in the presence of the homozygous p.Arg512 mutation [12, 18]. The RPGR gene, most frequently involved in cases of X-linked RP, is also being actively studied. In preclinical studies using the rd9 model, restoration of the RPGRORF15 reading frame with the CRISPR/Cas9 system under AAV control showed promising results [25, 26]. These and other models confirm the importance of developing diverse in vivo systems for testing gene therapy and identifying specific mechanisms of degeneration in different forms of RP.

X-linked RP

X-linked retinitis pigmentosa (XLRP) is one of the most severe forms of RP, characterized by early onset and rapid progression, accounting for up to 20% of all cases of the disease. Of the six identified XLRP loci, only RPGR and RP2 have been confirmed as causative genes. According to Guadagni et al. [27], a zebrafish model demonstrated the preservation of the functions of these genes and their role in photoreceptor ciliary transport. RPGR mutations account for approximately 70% of XLRP cases, with typical X-linked transmission and variable manifestations in female carriers [26–28]. Gene therapy using rAAV5, reviewed by Colombo et al. [29], showed improvement in visual function in dogs with an RPGR defect, including morphological restoration of the retina. RP2 mutations are responsible for 15% of XLRP cases and, in most cases, affect the cofactor C domain, disrupting protein localization [30–33]. At present, RP2 gene therapy remains experimental; however, the authors point to its potential with further development of delivery and expression methods. Thus, RPGR therapy already demonstrates clinical promise, whereas additional preclinical studies are required for RP2 [34–37].

Strategies for Targeted Correction of Genetic Disorders in Retinitis Pigmentosa

The identification of new genes involved in the pathogenesis of retinitis pigmentosa plays a key role in expanding the possibilities of gene therapy. In recent years, the analysis of sequencing data from large population cohorts has made it possible to establish a number of previously unknown genetic targets potentially responsible for the development of RP. Liu et al. [38], as well as Guimaraes and colleagues [36], emphasize that whole-genome sequencing has enabled the identification of new genes involved in degenerative retinal processes. Thus, Sp et al. [39] analyzed genetic variants in cohorts of patients from Israel and Palestine, which led to the identification of SLC66A1 and SLC39A12 as possible target genes. Vasudevan and his team [40] demonstrated that knockout of the SLC7A14 gene in mice causes retinal degeneration and reduced visual function, indicating its role in photoreceptor development. McClements and colleagues [35] also established that rare variants in the AGBL5 gene, such as p.Arg281Cys and p.Arg487*, may be associated with the development of RP [30]. Despite these findings, the authors agree that further studies are needed to clarify the exact pathophysiological role of these genes and their potential suitability for gene therapy. The overall conclusion confirms that the identification of new targets opens prospects for personalized treatment of RP based on the patient's molecular profile.

Future Prospects

The use of gene therapy with AAV vectors is actively developing in preclinical studies using mouse models, including models of retinitis pigmentosa. To date, only a few therapeutic approaches have reached the stage of clinical trials, with treatment for Leber congenital amaurosis type 2 remaining the most advanced; however, even in this case, a discrepancy is observed between improvement in visual function and long-term photoreceptor survival [10]. In RP therapy, this is especially important, since the main goal is not only stabilization of vision but also slowing the progressive degeneration of the retina [31]. Some limitations are associated with immune reactions to AAV vectors, particularly after repeated injections, which may also affect therapeutic efficacy in patients with RP [32]. In addition, the age of disease onset and the stage of degeneration at the time of treatment play a decisive role in determining the optimal therapeutic window. A personalized approach aimed at correcting a specific genetic defect in the early stages of RP may be the most effective, especially when AAV vectors are used to replace the lost function of a gene [33]. However, given the genetic heterogeneity of RP and the low prevalence of many forms of the disease, universal neuroprotective gene therapy strategies capable of slowing progression regardless of etiology are being actively investigated [18]. For patients with advanced stages of RP, when photoreceptor function has been lost, cell therapy, optogenetics, and retinal prostheses are considered promising, while viral vectors may be used to deliver sensitizing genes to inner retinal cells [40–42]. Issues of cell integration, differentiation, and the establishment of synaptic connections remain key challenges requiring deeper study of retinal biology for the successful clinical implementation of combined therapeutic approaches.

CONCLUSION

Retinitis pigmentosa remains one of the most complex and genetically heterogeneous forms of inherited retinal dystrophy, for which no universal pathogenetic treatment is still available. The development of gene therapy using viral vectors, particularly AAV, opens new possibilities for etiotropic intervention in various forms of RP. However, therapeutic efficacy depends significantly on the timing of treatment initiation, the molecular characteristics of the mutation, and the patient's immune response. Our study emphasizes the importance of precise molecular diagnosis and selection of the vector platform according to the type of genetic defect. In addition, the identified limitations in gene insert size when using AAV vectors require further optimization, including the development of dual and modified vector systems. The results of our analysis confirm the prospects of integrating viral vectors into personalized therapy regimens, especially at the early stages of degeneration. Thus, further expansion of in vivo models and targeted validation of candidate genes are key to improving the effectiveness of RP gene therapy in clinical practice.

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