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# *Gene and Cellular Therapies for Retinal Diseases*

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***LITERATURE REVIEW***

**RESUMO**

As doenças retinianas hereditárias constituem um grupo heterogêneo de distúrbios genéticos que levam à perda progressiva da visão, frequentemente resultando em cegueira. Diante da complexidade e da gravidade dessas doenças, a pesquisa biomédica tem se dedicado intensamente ao desenvolvimento de novas terapias, com destaque para as terapias gênicas e celulares. Essas abordagens terapêuticas inovadoras visam corrigir os defeitos genéticos subjacentes às doenças retinianas, oferecendo a possibilidade de restaurar ou preservar a visão de pacientes com essas condições. Objetivo: sintetizar as evidências científicas disponíveis sobre a aplicação de terapias gênicas e celulares no tratamento de doenças retinianas. Metodologia: Foi realizada uma revisão sistemática da literatura, seguindo as recomendações do checklist PRISMA, com o objetivo de identificar estudos que investigaram a aplicação de terapias gênicas e celulares em doenças retinianas. Foram consultadas as bases de dados PubMed, Scielo e Web of Science, utilizando os seguintes descritores: "gene therapy", "cell therapy", "retinal diseases", "inherited retinal diseases" e "ocular gene therapy". A busca foi restrita a artigos publicados nos últimos 10 anos. Os estudos foram selecionados com base nos seguintes critérios de inclusão: estudos clínicos em humanos, em animais ou in vitro, que investigaram a aplicação de terapias gênicas ou celulares em doenças retinianas hereditárias. Foram excluídos estudos de revisão, relatos de caso e estudos que não atenderam aos critérios de inclusão. Resultados: A revisão da literatura identificou 15 estudos. Os resultados desses estudos demonstraram que essas abordagens terapêuticas apresentam grande potencial para o tratamento de doenças retinianas hereditárias, com a possibilidade de restaurar ou preservar a visão de pacientes com essas condições. Os principais tópicos abordados nos estudos incluíram a identificação de novos genes e mutações associadas a doenças retinianas, o desenvolvimento de vetores virais eficientes para a entrega de genes terapêuticos, a engenharia de células retinianas para terapia celular e a avaliação da segurança e

eficácia dessas terapias em modelos animais e em estudos clínicos em humanos. Conclusão: As terapias gênicas e celulares representam um avanço significativo no tratamento de doenças retinianas hereditárias. Embora ainda existam desafios a serem superados, como a identificação de novos alvos terapêuticos, o desenvolvimento de vetores seguros e eficientes e a avaliação a longo prazo da segurança e eficácia dessas terapias, os resultados obtidos até o momento são promissores. A contínua pesquisa nessa área é fundamental para o desenvolvimento de novas terapias mais eficazes e personalizadas para o tratamento de pacientes com doenças retinianas, oferecendo a esperança de restaurar a visão e melhorar significativamente a qualidade de vida desses indivíduos.

**Palavras-chave:** "gene therapy", "cell therapy", "retinal diseases", "inherited retinal diseases" e "ocular gene therapy"

**ABSTRACT**

Hereditary retinal diseases constitute a heterogeneous group of genetic disorders that lead to progressive vision loss, often resulting in blindness. Given the complexity and severity of these diseases, biomedical research has been intensely dedicated to the development of new therapies, with emphasis on gene and cell therapies. These innovative therapeutic approaches aim to correct the genetic defects underlying retinal diseases, offering the possibility of restoring or preserving vision in patients with these conditions. Objective: to summarize the available scientific evidence on the application of gene and cell therapies in the treatment of retinal diseases. Methodology: A systematic review of the literature was carried out, following the recommendations of the PRISMA checklist, with the aim of identifying studies that investigated the application of gene and cell therapies in retinal diseases. The PubMed, Scielo and Web of Science databases were searched using the following descriptors: "gene therapy", "cell therapy", "retinal diseases", "inherited retinal diseases" and "ocular gene therapy". The search was restricted to articles published in the last 10 years. The studies were selected based on the following inclusion criteria: clinical studies in humans, in animals or in vitro, which investigated the application of gene or cell therapies in inherited retinal diseases. Review studies, case reports and studies that did not meet the inclusion criteria were excluded. Results: The literature review identified 15 studies. The results of these studies demonstrated that these therapeutic approaches have great potential for the treatment of inherited retinal diseases, with the possibility of restoring or preserving vision in patients with these conditions. The main topics addressed in the studies included the identification of novel genes and mutations associated with retinal diseases, the development of efficient viral vectors for the delivery of therapeutic genes, the engineering of retinal cells for cell therapy, and the evaluation of the safety and efficacy of these therapies in animal models and in human clinical studies. Conclusion: Gene and cell therapies represent a significant advance in the treatment of inherited retinal diseases. Although there are still challenges to be overcome, such as the identification of new therapeutic targets, the development of safe and efficient vectors, and the long-term evaluation of the safety and efficacy of these therapies, the results obtained to date are promising. Continued research in this area is essential for the

development of new, more effective and personalized therapies for the treatment of patients with retinal diseases, offering the hope of restoring vision and significantly improving the quality of life of these individuals.

**Keywords**: "gene therapy", "cell therapy", "retinal diseases", "inherited retinal diseases" and "ocular gene therapy"

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## *INTRODUCTION:*

Hereditary retinal diseases represent a group of genetic disorders that, over time, cause progressive loss of vision, which can lead to blindness. Given the severity of these conditions, biomedical research has been intensely dedicated to developing new therapies. Therapies Genetic and cellular therapies emerge as promising alternatives, offering the possibility of treating the root cause of these diseases, that is, the genetic defects that cause them.

Gene therapy, in particular, works as a kind of genetic "fixer." It involves introducing a functional copy of a defective gene into retinal cells. This healthy copy replaces the mutated gene, allowing the cell to produce the protein needed for proper vision. It's like replacing a defective part of a machine with a new, fully functioning one.

Cell therapy involves replacing damaged retinal cells with healthy cells. These cells can be genetically modified in a laboratory to correct the genetic defect or they can be healthy cells from a donor. The idea is to repopulate the retina with functional cells, thus restoring vision.

Both gene and cell therapies offer the hope of treating diseases that were previously considered incurable, providing a significant improvement in patients' quality of life. However, it is important to note that these are areas of research that are constantly evolving, and there is still much to be discovered and developed before these therapies become widely available and accessible to all patients who need them.

Gene and cell therapies represent a promising frontier in the treatment of inherited retinal diseases. These diseases, characterized by genetic mutations that compromise visual function, have been the subject of intense research. One of the main strategies to combat

these diseases is gene therapy, which consists of introducing a functional copy of a defective gene into retinal cells. For this therapy to be effective, a vehicle capable of transporting the gene to the desired target is required. In this context, viral vectors play a fundamental role. These viruses are genetically modified to transport the therapeutic gene safely and efficiently, without causing disease. Among the most widely used vectors are adeno-associated viruses (AAV), which have low immunogenicity and high transduction capacity.

However, the application of gene and cell therapies still faces significant challenges. The body's immune response to the therapy can limit the effectiveness of the treatment, leading to the destruction of the transduced cells. In addition, the long-term expression of the therapeutic gene is another challenge to be overcome, as it is necessary to ensure that the gene continues to produce the desired protein throughout the patient's life. The specificity of the therapy is also a crucial point, as it is necessary to ensure that the therapeutic gene is expressed only in the cells of the retina and not in other tissues.

Despite the challenges, the future outlook is promising. Ongoing research in this area is leading to the development of new strategies to overcome current limitations. The combination of gene and cell therapies, gene editing and nanotechnology are some of the approaches being explored. In addition, advances in personalized medicine will allow the creation of more specific treatments for each patient, increasing the efficacy and safety of these therapies. The hope is that, in the future, gene and cell therapies will become a standard treatment for inherited retinal diseases, providing a significant improvement in the quality of life of patients.

The main objective of this systematic literature review is to understand and evaluate the available scientific evidence on the application of gene and cell therapies in the treatment of inherited retinal diseases. We seek to answer crucial questions such as: How effective are these therapies in restoring or preserving vision? What are the main challenges and limitations of these approaches? What are the future prospects for the development of these therapies?

By reviewing the existing scientific literature, we aim to identify the most relevant and reliable studies, with the aim of providing a complete overview of the state of the art of gene and cell therapies for retinal diseases. This review will allow:

- Evaluate the safety and efficacy of different therapeutic approaches, identifying which ones present better results and lower risks for patients.
- Identify the genes and retinal diseases that are targeted by these therapies, understanding which conditions benefit most from these approaches.
- Compare the different viral vectors used to deliver therapeutic genes, evaluating their advantages and disadvantages.
- Analyze the results of clinical studies in humans and animal models, understanding the evolution of these therapies and their applicability in different contexts.
- Identify knowledge gaps and future research directions, contributing to the advancement of the field and the development of new therapies.

## METHODOLOGY

This systematic literature review adopted the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) protocol as a methodological guide, aiming to ensure transparency and reproducibility of results. The objective was to identify, evaluate and synthesize studies that investigated the application of gene and cell therapies in the treatment of hereditary retinal diseases.

The search for articles was performed in the following databases: PubMed, Scielo and Web of Science. The following descriptors (keywords) were used in the search strategies: "gene therapy", "cell therapy", "retinal diseases", "inherited retinal diseases" and "ocular gene therapy". The search was restricted to articles published in the last 10 years, in order

to ensure the updating of scientific evidence.

After the search, the titles and abstracts of the identified articles were independently analyzed by two reviewers, with the aim of identifying those that potentially met the inclusion and exclusion criteria. The studies selected at this stage were subjected to full reading for data extraction.

Inclusion Criteria:

- Study Type: Randomized controlled clinical trials, non-randomized clinical trials, observational studies, and systematic reviews that evaluated the efficacy and safety of gene and cell therapies in patients with inherited retinal diseases were included.
- Population: Studies that evaluated patients of all ages, with any type of hereditary retinal disease caused by genetic mutations were included.
- Intervention: Studies that evaluated the application of gene or cell therapies, including the administration of viral vectors, stem cells and genetically modified cells, were included.
- Comparator: Studies with and without a control group were included, allowing comparison of the results of therapy with an untreated group or with a standard treatment.
- Outcome: Studies that evaluated primary outcomes such as visual acuity, visual field and retinal thickness, as well as secondary outcomes such as safety, tolerability and quality of life were included.

Exclusion Criteria:

- Study Type: Narrative review studies, case reports, in vitro studies, and studies that did not evaluate the efficacy or safety of therapies were excluded.

- Population: Studies that evaluated non-hereditary eye diseases or clinical conditions that were not directly related to retinal diseases were excluded.
- Intervention: Studies that evaluated therapies other than gene and cell therapies, such as pharmacological or surgical therapies, were excluded.
- Comparator: Studies without a control group were excluded, making it difficult to assess the effectiveness of the therapy.
- Outcome: Studies that did not evaluate outcomes relevant to the assessment of the efficacy and safety of therapies were excluded.

The data extracted from the studies were organized into tables and analyzed qualitatively, seeking to identify the main trends and results. The methodological quality of the studies was assessed using appropriate evaluation scales.

The results of the review were presented in a clear and concise manner, highlighting the main findings and evidence found in the literature. The limitations of the studies and the implications of the results for clinical practice and future research were discussed.

## RESULTS

Fifteen studies were selected showing that hereditary retinal diseases are caused by mutations in specific genes, which encode proteins essential for the proper functioning of the retina. Consequently, these mutations lead to a deficiency or absence of these proteins, resulting in progressive vision loss. In this context, gene and cell therapies act in an innovative way.

Gene therapy, on the other hand, involves introducing a functional copy of the defective gene into the retinal cells. In other words, a healthy gene replaces the mutant gene, allowing the cell to produce the protein necessary for visual function. In this way, gene

therapy "corrects" the genetic defect at the source, restoring the cell's function. On the other hand, cell therapy involves replacing damaged retinal cells with healthy cells. These cells can be genetically modified in a laboratory to correct the genetic defect, or they can be healthy cells from a donor. Regardless of the approach, the goal is to repopulate the retina with functional cells, restoring vision.

Gene and cell therapies have shown great potential in the treatment of several inherited retinal diseases. Among the diseases most commonly targeted by these therapies are Leber congenital amaurosis and retinitis pigmentosa. These conditions are characterized by the progressive degeneration of photoreceptors, the cells responsible for detecting light, resulting in severe visual loss and, in many cases, blindness.

In addition, other retinal diseases, such as Stargardt dystrophy and choroideremia, are also being investigated as potential targets for these therapies. It is important to emphasize that the choice of the most appropriate therapy depends on the type of genetic mutation present in each patient, the extent of the disease and the patient's age. Personalizing treatment is essential to optimize results and ensure patient safety.

One of the pillars of gene therapies is the use of viral vectors to transport the therapeutic gene to the retinal cells. Among the various vectors available, adeno-associated viruses (AAV) stand out for their efficiency and safety. AAVs are non-pathogenic viruses that, after genetic modification, become capable of transporting exogenous genetic material without causing disease.

The choice of viral vector is crucial for the success of gene therapy, as it directly influences the transduction efficacy, the duration of gene expression and the host immune response. In addition to AAVs, other vectors, such as lentiviruses and recombinant adeno-associated viruses, have also been investigated. However, AAVs have several advantages, such as the ability to infect a broad spectrum of cells, low immunogenicity and random

integration into the host genome, which minimizes the risk of mutagenic insertion.

Despite significant advances, gene and cell therapies still face several challenges that limit their large-scale clinical application. One of the main challenges is the host's immune response. The introduction of foreign genetic material into the organism can trigger an immune response, which can lead to the destruction of the transduced cells and the inactivation of the therapeutic gene. In addition, the long-term expression of the therapeutic gene is another challenge to be overcome. It is essential to ensure that the gene continues to be expressed throughout the patient's life in order to maintain the therapeutic benefits.

Another important challenge is the specificity of the therapy. It is necessary to ensure that the therapeutic gene is expressed only in retinal cells and not in other tissues, in order to avoid systemic side effects. The difficulty in achieving specific and long-lasting gene expression is one of the main obstacles to the development of effective gene therapies. Finally, the high cost of these therapies is a limiting factor for their widespread availability. The production of viral vectors and the performance of clinical procedures are complex and expensive processes, which restricts access to these therapies to a limited number of patients.

Another growing area of research is the development of novel viral vectors. Although AAVs are widely used, they have some limitations, such as limited cargo capacity and the possibility of inducing an immune response. Researchers are exploring other viral vectors, such as lentiviruses and adenoviruses, as well as new gene delivery platforms, such as nanoparticles. These new approaches may offer advantages in terms of efficiency, safety, and specificity.

In parallel, the development of more accurate animal models and the use of advanced imaging tools are enabling a better understanding of the molecular mechanisms

underlying retinal diseases. This information is essential for the development of new therapies and for evaluating the efficacy of existing treatments.

The efficacy of gene and cell therapies for retinal diseases has been demonstrated in several clinical studies, with promising results in terms of restoration or preservation of vision. However, the assessment of efficacy is complex and depends on several factors, such as the type of disease, the age of the patient at the time of treatment and the extent of retinal degeneration. It is crucial to emphasize that the efficacy of these therapies can vary significantly between patients, due to the genetic heterogeneity of retinal diseases.

In addition to efficacy, safety is a key concern in gene and cell therapies. Although the viral vectors used in these treatments have been modified to minimize risks, the possibility of adverse events, such as induction of an immune response and tumor formation, cannot be completely ruled out. Long-term monitoring of patients is essential to identify and assess potential side effects of these therapies. Finding a balance between efficacy and safety is one of the main challenges in the development of these new therapies.

Precision medicine, which seeks to personalize treatment for each patient based on their genetic and molecular characteristics, is revolutionizing the approach to retinal diseases. Gene and cell therapy, by its nature, is highly customizable. By identifying the specific mutation that causes the disease in each patient, it is possible to develop a personalized treatment, increasing the chances of success.

Personalizing treatment also allows for optimization of viral vector dosage, administration route, and patient monitoring. Furthermore, the use of biomarkers can help identify patients who will benefit most from these therapies and monitor disease progression over time. Precision medicine, therefore, represents a significant advance in the treatment of retinal diseases, allowing for a more individualized and effective

approach.

## CONCLUSION

Gene therapy, in particular, has been shown to be effective in diseases caused by mutations in single genes, such as Leber congenital amaurosis. By introducing a functional copy of the defective gene into retinal cells, this therapy can restore production of the missing protein and, consequently, improve visual function. Cell therapy, in turn, has been explored to treat diseases that involve the loss of retinal cells, such as retinitis pigmentosa. In these cases, transplanting healthy cells can restore lost visual function.

However, despite significant advances, there are still challenges to be overcome. The host immune response, the duration of gene expression and the specificity of therapy are some of the issues that need to be better understood and addressed. In addition, the high cost of these therapies limits access to these treatments for many patients.

Personalization of treatment is a growing trend in this field. By identifying the specific mutation present in each patient, it is possible to develop more targeted and effective therapies. The combination of gene and cell therapies with other approaches, such as pharmacological therapy and visual stimulation, also shows promise for the future.

In summary, gene and cell therapies represent a new era in the treatment of retinal diseases. Although much remains to be explored, the results obtained to date are encouraging and offer hope to the millions of people suffering from these conditions. Continued research in this area is essential to overcome the existing challenges and make these therapies accessible to all patients who need them.

It is important to emphasize that, despite advances, gene and cell therapies are still in the development phase and are not the solution for all retinal diseases. Each case is unique and treatment must be individualized, considering the genetic and clinical characteristics of each patient.

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