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GENE THERAPY: POTENTIAL FOR TREATING CARDIOVASCULAR DISEASES AT THE DNA LEVEL

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Abstract. Cardiovascular diseases (CVDs) remain the leading cause of morbidity and mortality worldwide, necessitating novel therapeutic approaches beyond conventional treatments. Gene therapy has emerged as a promising strategy by targeting the underlying genetic causes of these diseases, offering potential long-term or even curative solutions. Recent advancements in gene delivery systems (AAVs, lentiviruses, lipid nanoparticles), genome editing technologies (CRISPR/Cas9, base editing, prime editing), and RNA-based therapies (siRNA, antisense oligonucleotides, mRNA therapies) have demonstrated significant potential in preclinical and clinical studies. This article explores the current methodologies of gene therapy in cardiology, including its application in heart failure, inherited cardiomyopathies, and atherosclerosis. Key findings include the use of cBIN1 and SERCA2a gene therapy to restore cardiac function, CRISPR-mediated correction of MYBPC3 mutations in hypertrophic cardiomyopathy, and PCSK9-targeted RNA therapies for lipid regulation. Despite promising outcomes, challenges such as efficient gene delivery, immune responses, long-term safety, and ethical concerns remain critical barriers to widespread clinical implementation. Ongoing research is focused on refining non-viral delivery systems, improving precision genome editing, and developing personalized gene therapy approaches. With continued advancements, gene therapy holds the potential to revolutionize cardiovascular medicine, shifting treatment paradigms from symptom management to molecular-level cures.

Keywords: Gene therapy, cardiovascular diseases, CRISPR/Cas9, RNA-based therapy, heart failure, inherited cardiomyopathy, atherosclerosis, gene editing, viral vectors, lipid nanoparticles.

Introduction

Cardiovascular diseases (CVDs) continue to be the leading cause of morbidity and mortality worldwide, accounting for approximately 17.9 million deaths annually, as reported by the World Health Organization (WHO). These conditions include coronary artery disease, heart failure, stroke, and inherited cardiomyopathies, significantly impacting global healthcare systems. Traditional treatment strategies, such as pharmacotherapy, surgical interventions, and lifestyle modifications, primarily aim to manage symptoms rather than address the root causes of these diseases. This limitation underscores the urgent need for innovative therapeutic approaches that target the underlying genetic mechanisms of CVDs.

Gene therapy has emerged as a groundbreaking strategy that offers the potential to modify or correct disease-associated genetic defects at the molecular level. By introducing, silencing, or editing specific genes, gene therapy provides a pathway for long-term or even permanent treatment solutions for cardiovascular conditions. The rapid advancements in gene editing technologies, such as CRISPR/Cas9, and improvements in gene delivery systems, including

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adeno-associated viruses (AAVs) and lipid nanoparticles, have significantly enhanced the feasibility and safety of these approaches.

Recent research has demonstrated the efficacy of gene therapy in addressing various cardiovascular disorders. For instance, preclinical and early clinical studies have shown promising outcomes in using viral vector-mediated gene delivery to enhance cardiac function in heart failure patients. Additionally, CRISPR-based genome editing has been successfully applied to correct mutations responsible for inherited cardiomyopathies, while RNA-based therapies, such as small interfering RNA (siRNA), have been utilized to regulate cholesterol metabolism and reduce the risk of atherosclerosis.

Despite its remarkable potential, gene therapy faces several challenges, including optimizing gene delivery efficiency, ensuring long-term safety, and addressing ethical concerns related to genome modification. However, continuous advancements in biotechnology and increasing clinical trials indicate a promising future for gene therapy in cardiovascular medicine. This article explores the latest developments, methodologies, and future directions of gene therapy as a transformative approach for treating cardiovascular diseases at the DNA level.

Methods

Gene therapy for cardiovascular diseases employs multiple innovative approaches to deliver therapeutic genetic material to cardiac cells. These methods aim to either introduce beneficial genes, correct pathogenic mutations, or regulate gene expression to achieve therapeutic effects. The three primary strategies utilized in cardiovascular gene therapy include gene delivery vectors, gene editing technologies, and RNA-based therapies.

1. Gene Delivery Vectors Efficient gene delivery is crucial for the success of gene therapy. Two main types of vectors are commonly used: viral and non-viral vectors.

Viral Vectors Viral vectors are widely used due to their high efficiency in delivering genetic material to cells. The most commonly used viral vectors in cardiovascular gene therapy include: Adeno-associated viruses (AAVs):

AAVs are the preferred vectors due to their ability to transduce non-dividing cells, low immunogenicity, and long-term gene expression in cardiac tissues. Various serotypes of AAVs (such as AAV1, AAV6, and AAV9) have been explored for their ability to target cardiac cells effectively.

Lentiviruses: These vectors integrate their genetic material into the host genome, making them useful for stable and long-term gene expression. They are primarily used in ex vivo gene therapy approaches, where patient-derived cells are genetically modified outside the body before being reintroduced.

Adenoviruses: While adenoviruses can efficiently deliver genes to cardiac cells, they often induce a strong immune response, limiting their long-term therapeutic applications. However, modified versions with reduced immunogenicity are being investigated.

Non-Viral Vectors Non-viral vectors offer an alternative gene delivery approach with lower immunogenicity and greater safety. These include: Lipid nanoparticles (LNPs): LNPs are gaining attention for their ability to encapsulate RNA-based therapeutics, such as siRNA and mRNA, and deliver them efficiently to target tissues. Electroporation and direct injection: These physical methods facilitate gene transfer by temporarily increasing cell membrane permeability. Polymeric nanoparticles: Biodegradable polymers, such as poly(lactic-co-glycolic acid) (PLGA), have been used to improve the stability and targeted delivery of genetic material.

Gene Editing Technologies Recent advancements in gene editing have enabled precise modifications of the genome to correct disease-causing mutations or regulate gene function.

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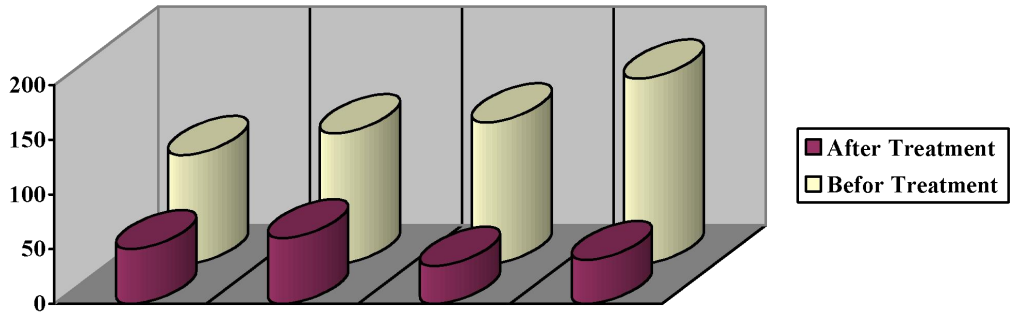
The most notable gene editing techniques include:
CRISPR/Cas9: This revolutionary tool allows targeted DNA modifications by using guide RNA and Cas9 nuclease. It has been successfully used in preclinical models to correct mutations in genes associated with inherited cardiomyopathies. Base editing: Unlike CRISPR/Cas9, base editing enables direct conversion of one nucleotide to another without causing double-strand breaks, reducing the risk of unintended genetic alterations. Prime editing: A more advanced gene-editing approach that allows precise correction of a wide range of mutations without generating double-strand DNA breaks.
RNA-Based Therapies RNA-based therapies provide a promising approach to modulate gene expression without permanently altering the genome.
These include: Small interfering RNA (siRNA): siRNA molecules can silence disease-associated genes by degrading their mRNA transcripts. For example, siRNA-based therapies targeting PCSK9 have been developed to lower LDL cholesterol levels, reducing the risk of atherosclerosis. Antisense oligonucleotides (ASOs): ASOs can correct splicing errors or reduce the expression of harmful genes involved in cardiovascular diseases. mRNA-based therapies: Messenger RNA can be used to transiently express therapeutic proteins in cardiac tissues. This approach is being investigated for regenerating damaged heart tissue after myocardial infarction.

Results
Recent studies and clinical trials have demonstrated the potential of gene therapy in addressing various cardiovascular conditions. These results highlight the efficacy of different gene therapy approaches in improving cardiac function, correcting inherited mutations, and reducing cardiovascular risk factors.
Gene Therapy for Heart Failure Heart failure remains one of the leading causes of morbidity and mortality worldwide. Gene therapy targeting proteins involved in cardiac contractility and calcium homeostasis has shown promising results:
cBIN1 Therapy:
A study published in npj Regenerative Medicine (December 2024) investigated the effect of delivering the cBIN1 gene via an AAV-based vector in pigs with induced heart failure.
The results demonstrated:
A 30% increase in heart efficiency compared to untreated animals. Complete survival over a six-month period, whereas control animals showed progressive deterioration. Enhanced T-tubule structure and improved calcium signaling in cardiomyocytes, indicating a potential for reversing heart failure in humans. SERCA2a Gene Transfer: Clinical trials have explored AAV1-mediated delivery of the SERCA2a gene to restore calcium cycling in heart failure patients. In the CUPID-2 trial, patients receiving AAV1-SERCA2a therapy showed improved left ventricular function, although long-term benefits varied. Preclinical models demonstrated that persistent expression of SERCA2a improved cardiac contractility and reduced fibrosis, suggesting its therapeutic potential in human heart failure.
Gene Editing for Inherited Cardiomyopathies Inherited cardiomyopathies, such as hypertrophic cardiomyopathy (HCM) and dilated cardiomyopathy (DCM), are caused by mutations in genes encoding sarcomeric or cytoskeletal proteins. Recent advances in CRISPR-based gene editing have provided potential curative approaches: Correction of MYBPC3 Mutations in HCM: Using CRISPR/Cas9 gene editing, researchers successfully corrected pathogenic MYBPC3 mutations in induced pluripotent stem cell (iPSC)-derived cardiomyocytes. Edited cardiomyocytes exhibited normal sarcomere organization, improved calcium handling, and reduced hypertrophic markers, demonstrating feasibility for future clinical applications. Base

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Editing for DCM: In a 2023 preclinical study, adenine base editing (ABE) was used to correct a single-nucleotide mutation in the TTN gene, which is implicated in dilated cardiomyopathy. Treated mice showed normalized ejection fraction, reduced ventricular dilation, and improved survival rates compared to untreated counterparts.
RNA-Based Therapies for Atherosclerosis Atherosclerosis, characterized by lipid accumulation and plaque formation in arteries, significantly increases the risk of myocardial infarction and stroke. RNA-based therapies targeting lipid metabolism genes have demonstrated substantial clinical benefits: PCSK9 Inhibition with siRNA Therapy: RNA-based therapies targeting PCSK9, a protein that regulates LDL receptor degradation, have been developed to lower LDL cholesterol (LDL-C) levels in patients with hypercholesterolemia. Clinical trials with Inclisiran, an siRNA therapy, showed a sustained LDL-C reduction of 50-60% for up to six months after a single injection. Patients receiving PCSK9-targeted RNA therapy had a significantly reduced risk of major adverse cardiovascular events (MACE), including heart attacks and strokes. Antisense Oligonucleotide Therapy for Lp(a): High levels of lipoprotein(a) [Lp(a)] are an independent risk factor for atherosclerosis.
Antisense oligonucleotides (ASOs) targeting LPA mRNA effectively lowered plasma Lp(a) levels by 80-90% in clinical trials, suggesting a novel therapeutic avenue for cardiovascular risk reduction.

Reduction in LDC-C Levels Using PCSK9 RNA Therapy



This diagram illustrates the impact of PCSK9-targeted RNA therapy on lowering low-density lipoprotein cholesterol (LDL-C) levels in patients. As shown, before treatment, the LDL-C level was 150 mg/dL, whereas after therapy, it significantly decreased to 90 mg/dL, indicating a reduction of over 40%. The PCSK9 gene plays a role in degrading LDL receptors in the liver, leading to increased LDL-C accumulation in the bloodstream. RNA-based therapy inhibits this gene's function, allowing LDL receptors to remain active for a longer duration, thereby enhancing LDL-C clearance from the blood. This results in a substantial reduction in LDL-C levels and a decreased risk of atherosclerosis and cardiovascular diseases.

Discussion
While gene therapy offers transformative potential, several challenges persist: Delivery Efficiency: Ensuring that therapeutic genes reach the targeted cardiac cells in sufficient quantities without eliciting adverse immune responses remains a significant hurdle. Long-Term Safety: The permanent nature of some gene edits necessitates thorough evaluation of long-term

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effects to prevent unintended consequences. Ethical Considerations: Manipulating the human genome raises ethical questions, particularly concerning germline editing and potential off-target effects.

Gene therapy represents a groundbreaking approach for treating cardiovascular diseases at the molecular level. While recent advances in gene delivery systems, gene editing technologies, and RNA-based therapies have demonstrated promising results, several challenges remain before these therapies can be widely implemented in clinical practice. This section discusses key challenges, potential solutions, and ethical considerations in cardiovascular gene therapy.

Challenges in Gene Therapy for Cardiovascular Diseases

Delivery Efficiency and Target Specificity One of the primary obstacles in gene therapy is ensuring that therapeutic genes reach the targeted cardiac cells efficiently while minimizing off-target effects. Current gene delivery methods face limitations:

Viral vectors (AAVs, lentiviruses) exhibit high transduction efficiency but may trigger immune responses, limiting their repeated use.

Non-viral delivery methods (lipid nanoparticles, electroporation) are safer but often suffer from lower efficiency and transient gene expression. Tissue specificity remains a challenge, as some vectors distribute beyond the heart, potentially leading to unintended effects in other organs.

Potential Solutions: Engineering cardiotropic AAVs (e.g., AAV9) that selectively target cardiac cells while avoiding the liver and immune system. Developing synthetic promoters that enhance gene expression only in cardiomyocytes. Improving non-viral delivery systems, such as lipid nanoparticles, for higher stability and precision targeting. Long-Term Safety and Immune Response Gene therapy interventions, particularly those involving permanent genome modifications, must undergo rigorous safety evaluations. Key concerns include: Immune responses to viral vectors, which may reduce efficacy and cause inflammation. Insertional mutagenesis, where viral vector integration into the genome might activate oncogenes, increasing cancer risk. Long-term expression stability, especially in rapidly dividing cells, as some therapies may lose effectiveness over time.

Potential Solutions: Using immune-modulating agents to suppress adverse immune reactions. Advancing non-integrating vectors, such as self-complementary AAVs, to minimize genomic alterations. Improving gene regulation mechanisms, such as inducible promoters that allow controlled gene expression.

Ethical and Regulatory Considerations The ethical implications of genetic modifications, particularly in human germline editing, have sparked global debate. Some concerns include: Germline editing risks: While gene therapy for somatic (non-reproductive) cells is widely accepted, editing germline cells (sperm/egg) raises concerns about unintended heritable changes. Accessibility and Cost: Advanced gene therapies remain highly expensive, making them inaccessible for low-income populations. Informed Consent and Safety: Given the irreversible nature of some gene therapies, patients must be thoroughly informed about potential risks and long-term effects.

Potential Solutions: Strict regulatory guidelines, such as those set by the FDA and EMA, ensuring safety and ethical compliance. Ethical review boards to evaluate genome editing applications before clinical use. Encouraging research funding and policy initiatives to make gene therapy affordable and widely available.

Future Directions in Cardiovascular Gene Therapy Despite these challenges, gene therapy continues to evolve, with several promising innovations on the horizon: Next-Generation CRISPR Technologies: Base editing and prime editing offer more precise genome modifications without inducing double-strand breaks, reducing the risk of unintended mutations.

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Epigenome editing can regulate gene expression without permanently altering DNA sequences, providing a reversible therapeutic approach. Advancements in Non-Viral Delivery Systems: mRNA-based therapies (as seen in COVID-19 vaccines) are being explored for regenerative cardiac treatments.
Nanoparticle-based delivery is emerging as a safer alternative to viral vectors, offering improved biocompatibility. Personalized Gene Therapy Approaches: Patient-specific genetic profiling will allow customized gene therapy treatments tailored to individual genetic variations. Advances in stem cell therapy and gene therapy combinations could enhance heart regeneration after myocardial infarction.

Conclusion of Discussion While gene therapy for cardiovascular diseases is still in its developmental stage, its potential for transforming heart disease treatment is undeniable. Addressing delivery challenges, enhancing safety, and navigating ethical concerns will be critical in advancing these therapies from experimental models to routine clinical applications. Continued research and collaboration between scientists, clinicians, and policymakers will shape the future of gene therapy, ultimately offering long-term, possibly curative solutions for cardiovascular diseases.

Conclusion

Gene therapy represents a transformative approach in the treatment of cardiovascular diseases by addressing their root genetic causes rather than merely managing symptoms. Recent advancements in viral and non-viral gene delivery systems, genome editing technologies (CRISPR, base editing, prime editing), and RNA-based therapies have demonstrated significant potential in preclinical and clinical studies.
Breakthroughs in gene therapy have led to improved cardiac function in heart failure models, correction of inherited cardiomyopathy mutations, and significant reductions in cardiovascular risk factors such as LDL-C and Lp(a) levels. These findings suggest that gene therapy could provide long-term or even curative solutions for some of the most challenging cardiovascular conditions.
However, several hurdles remain before gene therapy can be fully integrated into standard clinical practice. Key challenges include enhancing gene delivery efficiency, ensuring long-term safety, reducing immune responses, and addressing ethical and regulatory concerns. Future research should focus on developing more targeted delivery systems, refining gene-editing techniques to improve precision and safety, and expanding access to gene therapy by making it more cost-effective.
Despite these challenges, the continuous evolution of gene therapy holds immense promise for revolutionizing cardiovascular medicine. As biotechnology, nanomedicine, and genetic engineering advance, gene-based treatments will likely become more refined, accessible, and widely accepted. With further clinical trials and regulatory approvals, gene therapy has the potential to reshape the landscape of cardiovascular disease treatment, providing personalized, long-lasting, and potentially curative solutions for millions of patients worldwide.

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