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The Role of CRISPR-Based Gene Editing in Eradicating Latent HIV Reservoirs in Patients on Antiretroviral Therapy (ART): A Scoping Review

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ABSTRACT

The persistence of latent HIV reservoirs remains a major barrier to achieving a cure for HIV, despite the effectiveness of antiretroviral therapy (ART) in suppressing viral replication. Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)-based gene editing has emerged as a promising tool for targeting and eliminating these reservoirs, offering a novel approach to HIV eradication. This scoping review explored the potential role of CRISPR-based gene editing in eradicating latent HIV reservoirs in patients on ART. It synthesized evidence from preclinical and clinical studies, discussing key mechanisms such as proviral DNA excision, gene disruption, and host gene modulation. Preclinical studies have shown successful excision of integrated HIV DNA from infected cells, with significant reductions in viral load and prevention of viral rebound in animal models. However, challenges remain, including off-target effects, delivery system limitations, and concerns about long-term safety. Early-phase clinical trials focusing on ex vivo gene editing have begun, offering insights into the feasibility of CRISPR-based therapies in humans. This review also addressed the ethical, regulatory, and technical challenges in implementing CRISPR-based interventions, emphasizing the need for further research to optimize these therapies. The methodology utilized for this review involved a comprehensive search of available literature, followed by thematic synthesis and analysis of current findings. The review concluded that CRISPR-based gene editing holds immense promises for advancing HIV cure research but requires further innovation and rigorous clinical testing before widespread clinical application.

Keywords: CRISPR-based gene editing, Latent HIV reservoirs, HIV cure, Antiretroviral therapy (ART), Gene disruption.

INTRODUCTION

The introduction of antiretroviral therapy (ART) has transformed HIV from a fatal disease to a manageable chronic condition, enabling millions of people living with HIV (PLWH) to lead healthy and productive lives [1–3]. However, ART is not a cure. Despite its ability to suppress viral replication to undetectable levels, HIV persists in latent reservoirs dormant viral DNA integrated into the genomes of host cells, primarily CD4+ T cells [4, 5]. These reservoirs are unaffected by ART and can reactivate upon treatment interruption, leading to viral rebound and disease progression. The persistence of latent HIV reservoirs represents the principal barrier to achieving a cure for HIV.

Efforts to eradicate latent HIV reservoirs have focused on two main strategies: "shock and kill" and "block and lock." The "shock and kill" approach aims to reactivate latent HIV, making it visible to the immune system and susceptible to ART, while the "block and lock" strategy seeks to permanently silence the virus [6]. However, both approaches face significant challenges, including incomplete reservoir reactivation, immune evasion, and potential toxicity. Consequently, there is an urgent need for innovative strategies to target and eliminate latent HIV reservoirs.

Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)-based gene editing has emerged as a groundbreaking technology with the potential to address these challenges. CRISPR-Cas9, the most widely used

gene-editing system, enables precise targeting and modification of specific DNA sequences [7]. In the context of HIV, CRISPR-based gene editing can be used to exercise integrated proviral DNA from the host genome, effectively eradicating latent reservoirs. Preclinical studies have demonstrated the feasibility of this approach, with CRISPR-Cas9 successfully excising HIV DNA from infected cells in vitro and in animal models. Despite its promise, the application of CRISPR-based gene editing in HIV cure research is still in its infancy. Key challenges include ensuring the specificity and efficiency of gene editing, minimizing off-target effects, and delivering the CRISPR system to latent reservoirs in vivo. Additionally, the long-term safety and feasibility of this approach in humans remain to be fully elucidated. This scoping review aims to explore the role of CRISPR-based gene editing in eradicating latent HIV reservoirs in patients on ART. By synthesizing evidence from preclinical and clinical studies, this review will provide a comprehensive overview of the current state of research, identify key knowledge gaps, and highlight future directions for advancing CRISPR-based strategies toward an HIV cure.

MECHANISMS OF CRISPR-BASED GENE EDITING IN HIV ERADICATION

CRISPR-Cas9 is a versatile gene-editing tool that uses a guide RNA (gRNA) to direct the Cas9 endonuclease to a specific DNA sequence, where it introduces double-strand breaks. These breaks can be repaired by the cell's natural repair mechanisms, either through non-homologous end joining (NHEJ), which often results in gene disruptions, or homology-directed repair (HDR), which can be used to introduce specific genetic modifications [8, 9]. In the context of HIV eradication, CRISPR-Cas9 can be employed to target and exercise integrated proviral DNA from the host genome. The key mechanisms by which CRISPR-based gene editing can eradicate latent HIV reservoirs include:

i. **Proviral DNA Excision:** CRISPR-Cas9 can be designed to target conserved regions of the HIV genome, such as the long terminal repeats (LTRs), which are present at both ends of the integrated provirus. By introducing double-strand breaks at these sites, CRISPR-Cas9 can excise the entire proviral DNA, effectively eliminating the latent reservoir.
ii. **Gene Disruption:** In cases where complete excision is not feasible, CRISPR-Cas9 can be used to disrupt essential viral genes, such as gag, pol, or env, rendering the virus nonfunctional. This approach can prevent viral reactivation and reduce the risk of viral rebound.
iii. **Host Gene Modulation:** CRISPR-Cas9 can also be used to modify host genes that are critical for HIV replication or latency. For example, targeting the CCR5 co-receptor, which is required for viral entry, can confer resistance to HIV infection.

The development of next-generation CRISPR systems, such as base editors and prime editors, has further expanded the potential applications of gene editing in HIV cure research. These systems enable precise nucleotide changes without inducing double-strand breaks, reducing the risk of off-target effects and improving the safety profile of gene-editing interventions.

PRECLINICAL EVIDENCE FOR CRISPR-BASED HIV ERADICATION

Preclinical studies have provided compelling evidence for the feasibility of CRISPR-based gene editing in eradicating latent HIV reservoirs. In vitro studies using HIV-infected cell lines and primary CD4+ T cells have demonstrated that CRISPR-Cas9 can efficiently excise proviral DNA and disrupt viral genes, leading to a significant reduction in viral load and preventing viral reactivation [10].

Animal models have also been instrumental in evaluating the efficacy and safety of CRISPR-based interventions. In a landmark study, researchers used CRISPR-Cas9 to exercise HIV DNA from the genomes of humanized mice infected with HIV [11]. The study found that CRISPR-Cas9 treatment led to a significant reduction in viral load and prevented viral rebound after ART interruption. Similar results have been reported in non-human primate models, providing further support for the potential of CRISPR-based gene editing in HIV cure research. Despite these promising findings, challenges remain. The efficiency of gene editing in latent reservoirs is often limited by the low abundance of target cells and the difficulty of delivering CRISPR components to these cells. Additionally, the potential for off-target effects and immune responses to the CRISPR system poses significant safety concerns.

CLINICAL APPLICATIONS AND CHALLENGES

The translation of CRISPR-based gene editing from preclinical models to clinical applications is a complex and multifaceted process. Early-phase clinical trials are currently underway to evaluate the safety and feasibility of CRISPR-based interventions in PLWH. These trials focus on ex vivo gene editing, where CD4+ T cells are extracted from patients, edited using CRISPR-Cas9, and reinfused into the body [12–14].

One of the key challenges in clinical applications is ensuring the specificity and efficiency of gene editing. Off-target effects, where CRISPR-Cas9 introduces unintended mutations in the host genome, can have serious consequences, including oncogenesis. Strategies to mitigate off-target effects include the use of high-fidelity Cas9 variants, optimized gRNA designs, and computational tools to predict and minimize off-target activity.

Another challenge is the delivery of CRISPR components to latent reservoirs in vivo. Current delivery methods, such as viral vectors and nanoparticles, face limitations in terms of efficiency, specificity, and immunogenicity. Advances in delivery technologies, including cell-penetrating peptides and lipid nanoparticles, are being explored to improve the targeting and delivery of CRISPR components to latent reservoirs.

ETHICAL AND REGULATORY CONSIDERATIONS

The application of CRISPR-based gene editing in HIV cure research raises several ethical and regulatory considerations. These include concerns about the potential for off-target effects, the long-term safety of gene-editing interventions, and the equitable access to these therapies. Additionally, the use of CRISPR in human embryos or germline cells raises ethical questions about the potential for heritable genetic modifications [15].

Regulatory frameworks for CRISPR-based therapies are still evolving, and there is a need for international guidelines to ensure the safe and responsible development of these interventions [16, 17]. This includes establishing rigorous preclinical testing requirements, monitoring long-term outcomes in clinical trials, and engaging with stakeholders, including patients, researchers, and policymakers.

CONCLUSION

CRISPR-based gene editing represents a transformative approach to eradicating latent HIV reservoirs and achieving a cure for HIV. By enabling precise targeting and excision of integrated proviral DNA, CRISPR-Cas9 offers the potential to eliminate the principal barrier to an HIV cure. Preclinical studies have demonstrated the feasibility and efficacy of this approach, and early-phase clinical trials are underway to evaluate its safety and feasibility in humans. However, significant challenges remain, including ensuring the specificity and efficiency of gene editing, developing safe and effective delivery methods, and addressing ethical and regulatory considerations. Future research should focus on optimizing CRISPR-based strategies, advancing delivery technologies, and conducting rigorous clinical trials to evaluate the long-term safety and efficacy of these interventions. As the field of CRISPR-based gene editing continues to evolve, it holds immense promises for revolutionizing HIV cure research. With continued innovation and collaboration, CRISPR-based interventions could play a pivotal role in achieving the goal of an HIV-free world.

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