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Zinc Finger Nuclease-Mediated CCR5 Disruption as Host-Directed Therapy Against HIV Infection

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ABSTRACT

Human immunodeficiency virus infection remains a major global health challenge despite major advances in antiretroviral therapy. Current treatment requires lifelong drug administration and does not eliminate latent viral reservoirs, creating a persistent need for innovative therapeutic strategies capable of achieving durable viral control. Viral entry into CD4-positive T lymphocytes requires interaction between the viral envelope glycoprotein and host cell receptors, including the chemokine receptor CCR5, which served as a principal co-receptor during early infection. The purpose of this review was to evaluate zinc finger nuclease-mediated disruption of the CCR5 gene as a host-directed therapeutic approach for long-term control of HIV infection. A structured narrative review methodology was used to synthesize findings from peer-reviewed studies addressing molecular mechanisms, gene editing efficiency, and therapeutic outcomes of CCR5-targeted zinc finger nuclease strategies. Evidence indicates that zinc finger nuclease-induced CCR5 disruption generated HIV resistant immune cells and can produce sustained persistence of modified lymphocytes in experimental and clinical settings. Gene-edited cells exhibit reduced susceptibility to viral entry and may contribute to partial control of viral replication. Zinc finger nuclease-mediated CCR5 disruption represented a promising host-directed therapeutic strategy with potential to reduce dependence on lifelong antiretroviral therapy. Continued clinical investigation and optimization of gene editing delivery systems were recommended to advance this approach toward durable HIV control.

Keywords: HIV infection, CCR5 receptor, Zinc finger nucleases, Gene editing, Host-directed therapy.

INTRODUCTION

Human immunodeficiency virus infection continues to represent a major global public health problem, with millions of individuals requiring lifelong treatment to maintain viral suppression [1, 2]. Antiretroviral therapy has transformed HIV infection into a manageable chronic disease by effectively inhibiting viral replication and preventing disease progression [3]. However, these therapies do not eliminate integrated proviral DNA or latent viral reservoirs, making permanent cure difficult to achieve. Viral rebound typically occurs following treatment interruption, highlighting the limitations of current therapeutic strategies. Consequently, increasing attention has focused on host-directed interventions that may provide durable resistance to infection.

HIV entry into susceptible cells requires coordinated interactions between viral envelope proteins and host cell receptors. Binding of the viral glycoprotein gp120 to the CD4 receptor initiates conformational changes that allow interaction with chemokine co-receptors, primarily CCR5, during early stages of infection [4]. Individuals carrying naturally occurring CCR5 gene mutations demonstrate strong resistance to HIV infection, indicating that disruption of CCR5 function can provide effective protection against viral entry. These observations have provided a strong rationale for therapeutic strategies aimed at eliminating CCR5 expression in susceptible immune cells [5].

Zinc finger nucleases represent one of the earliest gene editing technologies developed for targeted modification of human genes [6]. These engineered nucleases can introduce site-specific double-strand breaks within genomic DNA, leading to disruption of gene function through error-prone repair mechanisms. This review examines the molecular basis of HIV entry and the role of CCR5, the gene editing mechanisms of zinc finger nucleases, the cellular consequences of CCR5 disruption, experimental and clinical evidence supporting this approach, and the therapeutic opportunities and limitations associated with zinc finger nuclease-mediated CCR5 disruption. The purpose of this study is to evaluate zinc finger nuclease-mediated CCR5 gene disruption as a host-directed therapeutic strategy for achieving long-term control of HIV infection.

Molecular Basis of HIV Entry and the Role of CCR5

HIV infection begins with entry of the virus into susceptible host cells, primarily CD4-positive T lymphocytes and macrophages [7]. Viral entry is mediated by the envelope glycoprotein complex composed of gp120 and gp41. The gp120 subunit is responsible for initial attachment to the CD4 receptor, while gp41 mediates fusion between viral and cellular membranes.

Binding of gp120 to CD4 induces structural rearrangements that expose binding sites for chemokine co-receptors [8]. CCR5 serves as the principal co-receptor for viral entry during early infection and is highly expressed on activated T lymphocytes and macrophages. Interaction between gp120 and CCR5 stabilizes the envelope complex and promotes additional conformational changes that activate gp41-mediated membrane fusion. Membrane fusion allows the viral core to enter the cytoplasm, initiating the replication cycle. The requirement for CCR5 in early infection explains why viruses that utilize this co-receptor predominate in newly infected individuals. Cells lacking functional CCR5 receptors are resistant to infection by CCR5-tropic viral strains.

The biochemical importance of CCR5 is illustrated by individuals carrying the CCR5 delta 32 mutation, which produces a truncated receptor that fails to reach the cell surface. Homozygous carriers exhibit strong resistance to HIV infection [9], while heterozygous individuals demonstrate slower disease progression. These observations provide compelling evidence that elimination of CCR5 expression represents a viable therapeutic strategy. Because CCR5 is not essential for normal immune function, targeted disruption of the receptor is considered biologically tolerable. This feature makes CCR5 an attractive target for gene editing-based therapeutic approaches aimed at preventing viral entry [10].

Zinc Finger Nucleases: Molecular Design and Gene Editing Mechanisms

Zinc finger nucleases are engineered proteins designed to introduce targeted modifications within genomic DNA [11]. Each zinc finger domain consists of a small protein motif stabilized by coordination of a zinc ion and capable of recognizing specific nucleotide triplets. Multiple zinc finger domains can be linked together to generate DNA-binding proteins with high sequence specificity. The DNA-binding region is fused to the catalytic domain of the FokI restriction endonuclease. The FokI nuclease domain is inactive as a monomer and requires dimerization to produce a double-strand break [12]. Two zinc finger nuclease monomers bind to adjacent DNA sequences, allowing FokI domains to dimerize and cleave the intervening DNA segment.

Following double-strand break formation, cellular repair pathways are activated. Non-homologous end joining is the predominant repair mechanism in mammalian cells and frequently introduces insertions or deletions at the cleavage site. These mutations often disrupt the reading frame of the targeted gene, leading to loss of protein expression.

Targeting zinc finger nucleases to the CCR5 gene allows selective disruption of receptor expression in edited cells [13]. The efficiency of gene disruption depends on DNA binding specificity, nuclease activity, and cellular repair processes. Optimization of zinc finger arrays has improved targeting precision and reduced unintended genomic modifications. Gene editing is typically performed ex vivo by introducing zinc finger nuclease constructs into isolated immune cells or hematopoietic stem cells. Modified cells are expanded and reinfused into patients, where they can repopulate the immune system with HIV resistant cells. This approach provides a mechanistic basis for long-term therapeutic benefit.

CCR5 Gene Disruption and Cellular Resistance to HIV

Disruption of the CCR5 gene produces immune cells that are resistant to infection by CCR5-tropic HIV strains [14]. Zinc finger nuclease-mediated gene editing introduces mutations that prevent expression of functional CCR5 receptors on the cell surface. Without CCR5, viral entry cannot proceed efficiently despite successful binding to the CD4 receptor. The protective effect of CCR5 disruption closely resembles that observed in individuals carrying the naturally occurring CCR5 delta 32 mutation. Edited CD4-positive T lymphocytes demonstrate markedly reduced susceptibility to viral infection in vitro [15]. Resistance to infection allows these cells to survive and expand in the presence of ongoing viral replication.

Gene editing of hematopoietic stem cells offers the possibility of generating a continuous supply of HIV resistant immune cells. Stem cell-derived lymphocytes maintain disrupted CCR5 expression and provide long-term protection against viral entry [16]. Stable integration of gene editing modifications ensures persistence across multiple cell generations.

CCR5 disruption may also influence immune responses beyond prevention of viral entry [17]. Preservation of CD4-positive T cell populations supports maintenance of adaptive immunity and reduces immune system deterioration. Expansion of resistant cells during viral replication may gradually shift the immune cell population toward HIV resistant phenotypes. These cellular effects suggest that CCR5 disruption could provide sustained control of viral replication even without continuous pharmacologic therapy. However, incomplete editing efficiency may limit the proportion of resistant cells generated in treated individuals.

Preclinical and Clinical Evidence of Zinc Finger Nuclease CCR5 Therapy

Preclinical studies have demonstrated effective CCR5 disruption in cultured CD4-positive T cells using zinc finger nucleases [18]. Edited cells show substantial reductions in CCR5 expression and strong resistance to HIV infection. Experimental infection models confirm that modified cells maintain viability and function despite exposure to virus. Animal studies have provided further support for this approach. Transplantation of zinc finger nuclease-modified immune cells into immunodeficient mice produces stable engraftment and persistence of CCR5-disrupted cells [19]. These cells retain resistance to viral infection and contribute to partial control of viral replication.

Early clinical trials have evaluated the safety and feasibility of zinc finger nuclease-mediated CCR5 disruption in individuals with chronic HIV infection [20]. Autologous CD4-positive T cells are collected, genetically modified ex vivo, and reinfused into patients. Modified cells persist in circulation for extended periods and maintain reduced CCR5 expression.

Clinical studies demonstrate that zinc finger nuclease-modified cells are generally well tolerated with no major treatment-related toxicities. Some participants exhibit modest reductions in viral load during treatment interruption, suggesting partial restoration of immune control. Persistence of edited cells correlates with improved immunological parameters in certain individuals. Although clinical responses have been variable, these studies establish proof of concept for CCR5-targeted gene editing therapy. Larger clinical trials will be necessary to determine the magnitude and durability of therapeutic benefit.

Therapeutic Potential, Limitations, and Future Directions

Zinc finger nuclease-mediated CCR5 disruption represents a promising host-directed approach to HIV therapy [20]. By eliminating a critical entry receptor, this strategy directly interferes with viral infection at the earliest stage of the replication cycle. Gene-edited immune cells may provide long-lasting protection and reduce dependence on continuous antiretroviral therapy. Potential advantages include durable gene modification and selective resistance to infection without ongoing drug exposure. Expansion of resistant immune cells could gradually enhance immune control of viral replication. This approach may contribute to the development of a functional cure in which viral replication remains suppressed without continuous treatment.

Off-target cleavage by zinc finger nucleases may introduce unintended genomic alterations with potential safety consequences [21, 22]. Improvements in nuclease specificity are required to minimize these risks. Efficient delivery to hematopoietic stem cells remains technically demanding and may limit widespread application. Gene editing procedures require specialized facilities and are associated with high costs.

Future research should focus on improving editing efficiency, enhancing specificity, and developing scalable delivery systems. Combination approaches integrating gene editing with antiretroviral therapy or immune-based interventions may further improve outcomes.

CONCLUSION

Zinc finger nuclease-mediated disruption of the CCR5 gene provides a mechanistically rational host-directed strategy for long-term control of HIV infection. By eliminating expression of a critical viral entry receptor, gene-edited immune cells acquire resistance to infection and may persist as a stable population capable of supporting immune function. The biological rationale for this approach is supported by natural CCR5 mutations that confer resistance to HIV infection in humans. Advances in gene editing technology have enabled efficient disruption of CCR5 in immune cells and hematopoietic progenitors. Preclinical investigations demonstrate strong protection against viral infection, while early clinical studies confirm feasibility and acceptable safety profiles. Persistence of modified cells and evidence of partial viral control indicate meaningful therapeutic potential. Despite promising results, important challenges remain, including optimization of delivery methods, improvement of gene editing precision, and demonstration of durable clinical benefit. Continued translational research will be essential for realizing the full potential of this strategy. Zinc finger nuclease-mediated CCR5 disruption should be advanced through large-scale clinical trials as a host-directed strategy for achieving durable control of HIV infection.

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