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Recent Advances in Gene Editing Cargo Delivery for Hematopoietic Stem and Progenitor Cells

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Abstract: As the cornerstone of human hematopoiesis, hematopoietic stem and progenitor cells (HSPCs) sustain immune homeostasis by continuously generating blood cellular components. Their proliferative capacity and multilineage differentiation potential make them prime targets for gene therapy. The clinical application of HSPC genome editing relies on two key advancements: the development of highly specific and biocompatible genome-editing reagents and the establishment of efficient delivery systems ensuring targeted cellular uptake. Recent innovations in gene editing tools and cargo delivery methods, such as RNA- and protein-based editors, have enabled novel therapeutic strategies for hematological disorders. Current gene delivery platforms for HSPCs include electroporation, synthetic nanoscale carriers (e.g., polymeric and lipid nanoparticles), and engineered viral vectors such as integration-defective lentiviral vectors (IDLVs), adeno-associated viral vectors (AADVs), virus-like particles, and adenovirus vectors (AdVs). While ex vivo gene therapy remain predominant, it requires complex and costly patient conditioning regimens. in vivo approaches, primarily utilizing AdVs and LNPs, offer an alternative but lack sufficient targeting precision and transfection efficiency. By critically analyzing these advancements, this review aims to identify pathways for optimizing genome editing in HSPCs and enhancing therapeutic precision in hematological disorder management.

Keywords: Gene therapy, gene editing, gene delivery, hematopoietic stem and progenitor cells, blood disorders

1. Introduction

A variety of tissues in the adult human body maintain a limited population of adult stem cells, which play essential cytoprotective roles in preserving and replenishing specific cell types, thereby ensuring tissue homeostasis [1]. Among them, blood cells perform vital functions, including immune defense and injury repair. However, significant loss of blood cells can occur due to disease or trauma. Hematopoietic stem cells (HSCs) serve as the fundamental units of hematopoiesis, possessing lifelong capacity for blood system reconstitution. They exhibit two key functional attributes: clonal expansion potential and multilineage differentiation commitment. As adult stem cells, HSCs can replenish all types of blood cells, maintaining hematopoietic homeostasis [2]. Hematopoietic stem cell transplantation (HSCT) is the standard treatment for malignant hematological diseases and congenital disorders. In the 1950s, Rekers et al. carried out the technique of allogeneic HSCT by intravenously delivering bone marrow cells to irradiated mice, thereby preventing their demise and reconstituting hematopoiesis [3]. As of 2022, the global number of HSCT procedures has surpassed

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1.5 million [4]. However, allogeneic HSCT is not always the optimal treatment option due to its reliance on a highly matched human leukocyte antigen (HLA) profile. The probability of identifying a suitably matched sibling donor is less than 30%. Furthermore, allogeneic transplantation carries the risk of inducing immune rejection, which can result in severe complications or mortality [5,6]. To overcome these challenges, genetic modification of autologous HSCs has emerged as a promising strategy for treating hematological diseases. This approach involves either *ex vivo* gene editing followed by transplantation or direct *in vivo* gene therapy, aiming to correct disease-causing mutations while minimizing immune complications. This review focuses on recent advancements in gene editing cargo delivery for HSPCs, discussing efficient and safe delivery strategies, associated challenges, and existing solutions.

2. Gene Editing Cargo for HSPCs

A cell's physiological state is primarily determined by its genetic makeup. Therefore, a key goal in medical research is to precisely modify genetic loci and repair damaged genes. Transient genome-editing activation minimizes off-target effects and reduce editor immunogenicity [7]. For efficient "hit-and-run" genetic modifications, gene-editing cargos are best delivered as proteins or RNA. Jennifer Doudna et al. demonstrated that Cas9 recognizes its target sequence through the seed region within crRNA and requires a downstream protospacer-adjacent motif (PAM) for binding. Engineered RNAs can be custom-designed to direct Cas9 endonuclease activity toward predetermined loci, triggering programmable double-stranded DNA breaks through site-specific cleavage [8]. Expanding on this fundamental work, Feng's laboratory successfully adapted the CRISPR-Cas9 system for efficient genome editing in mammalian cells [9]. The gene-editing payload of CRISPR systems, including Cas9 nucleases delivered in mRNA form, has gained significant traction owing to recent advancements in mRNA technology and the advent of more complex gene editors such as base editors (approximately 4.8 kb) and prime editors (approximately 6.7 kb). These editors incorporate effectors fused with Cas9 variants [10,11]. Base editor mRNA achieves editing efficiencies exceeding 80% across various targets in HSPCs. Additionally, chemical modifications to the gene-edited mRNA further enhance the overall gene editing efficiency [10]. Nucleases can also be delivered directly in their protein form, which facilitates immediate action and rapid cellular turnover, thereby minimizing off-target effects. Currently, one of the most efficient and safe CRISPR-Cas9 gene editing strategies for human stem and progenitor cells involves the simultaneous delivery of pre-assembled ribonucleo-protein complexes (RNP), guided by RNA (gRNA) and Cas9 nuclease, via nucleofection. Moreover, RNP-based approaches do not compromise the survival capacity, clonal expansion potential, and post-transplantation functionality of HSPCs. Additionally, transient gene editing using RNPs minimizes off-target effects, insertion mutagenesis, and immune activation while achieving high editing efficiency.

3. Cargo Delivery Systems to HSPCs

AT primary challenge in delivering gene editors and DNA templates to HSCs, both *ex vivo* and *in vivo*, is ensuring efficient and safe genome editing. This is critical to maintaining accurate genetic information in the progeny of these cells. The selection of a delivery system depends on several factors, including the cellular repair pathway involved in editing, the required editing efficiency, the cytotoxicity tolerance of target cells, and the size of the donor DNA template. Current gene-editing delivery strategies can be broadly categorized into viral and non-viral methods. Among non-viral approaches, researchers are actively exploring physical and chemical methods for delivering biomolecular proteins and RNA.

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3.1. Electroporation

Electroporation is one of the most effective techniques for delivering biomolecule into cells. It enables efficient intracellular transport of mRNA and protein complexes, making it a powerful tool for gene editing. Additionally, it facilitates multiple gene editing across various target loci by delivering mRNA or RNPs [12-14]. The mechanism of electroporation involves transient disruption of membrane semi-permeability upon exposure to an electrical impulse, allowing RNA or RNP to enter the cell. Efficient homology-directed repair (HDR) relies on the concurrent delivery of donor DNA, nuclease, and sgRNA. Electroporation has been demonstrated to efficiently introduce these three components, facilitating HDR in stem cells. A key advantage of electroporation is its ability to deliver large molecular constructs, including Cas9 fusion proteins, base editors, and prime editors. While electroporation can induce transcriptional changes in human stem cells, their core pluripotency markers and trilineage differentiation potential remain unaffected. Early clinical studies indicate that patients with thalassemia and sickle cell disease, who previously required regular blood transfusions, have achieved transfusion independence [15].

3.2. Nanoparticles

Cationic/ionizable polymer nanoparticles (PNPs) and lipid nanoparticles (LNPs) can encapsulate negatively charged nucleic acids, facilitating intracellular delivery through various endocytosis mechanisms. These nanoparticles are easy to construct, exhibit low immunogenicity and non-invasiveness, enable rapid gene expression, and can be customized for cell- or tissue-specific delivery. For instance, studies have demonstrated effective silencing of CD44 protein expression in CD34+ acute myeloid leukemia (AML) cells using CD44 siRNA encapsulated in PNPs. This suggests that PNPs hold potential for targeting HSPCs [16]. Additionally, Cas9 RNPs encapsulated in poly β-amino esters (PBAE-PNPs) have achieved gene-editing efficiencies of up to 70% in HSPCs when targeting the CD33 and HBG promoters [17]. Notably, PNPs achieved equivalent gene-editing efficiency with only one-third of the Cas9 RNP dose required for electroporation, indicating their potential as a superior alternative [17].

3.3. Adeno-associated Viral Vectors

Adeno-associated virus vectors (AAVs) are among the most clinically validated gene therapy vehicles, with several FDA-approved gene therapy products. Their ability to transduce both dividing and non-dividing cells, coupled with stable transgene expression and a favorable safety profile, positions AAVs as leading vectors for *in vivo* gene therapy. AAV-based approaches have been utilized to treat various genetic disorders, including hereditary retinal dystrophy and hemophilia [18]. At least ten AAV serotypes have been identified, each exhibiting distinct cell-type specificity. Among these, AAV6 demonstrates a high affinity for HSCs. Modifications to AAV6 vectors have been shown to enhance transduction efficiency [19]. AAV6 has emerged as a leading viral vector for site-specific gene integration in *ex vivo* HSC therapies, and has been successfully utilized to correct a range of genetic diseases [20-23]. Triple mutation of the AAV6 capsid, combined with high-cell-confluence transduction conditions, has achieved over 90% transduction efficiency in HSPCs [24]. Despite these advantages, AAV-mediated gene therapy faces limitations due to its relatively small cargo capacity (approximately 4.7 kb). To address this limitation, researchers have explored dual-vector strategies and oversized AAV constructs to accommodate larger transgenes [25,26]. However, immune responses targeting AAV-transfected cells poses extra challenges that may constrain therapeutic efficacy [27].

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3.4. Integration Defective Lentiviral Vectors

Lentiviral vectors (LVs) represent another class of viral vectors widely utilized for gene editing. These vectors, originally derived from the HIV-1 envelope, have undergone modifications to enhance biosafety, including the removal of replication and integrase-related genes. LVs are predominantly employed for *ex vivo* delivery and offer a substantial cargo capacity (up to approximately 10kb), making them suitable for delivering Cas proteins and multiple sgRNAs, thereby enabling multi-gene editing.

However, conventional lentiviral vectors pose a risk of genomic integration, leading to sustained expression of gene-editing components and increased off-target indel rates [28-30]. To mitigate this risk, researchers developed integration-defective lentiviral vectors (IDLVs), which incorporate a trans-complementing packaging system and a point mutation in the integrase domain. The IDLV integrase protein interacts with the host cell protein LEDGF/p75 to facilitate homology-directed repair (HDR) in human embryonic stem cells (hESCs) [31]. Additionally, IDLV systems enable efficient HDR in HSPCs with reducing DNA damage signaling and minimizing the integration of viral sequences at target sites compared to AAV6-mediated delivery [32]. IDLVs have been successfully utilized for delivering zinc finger nuclease (ZFNs) and for introducing corrective DNA templates into HSPCs, especially in the context of Primary Immunodeficiency (PIDs) [33].

3.5. Virus-like Particles

While lentiviral vectors enable robust delivery of CRISPR components in HSPCs, the sustained nuclease activity resulting from persistent Cas9-gRNA expression elevates the risk of off-target mutagenesis. Delivering gene-editing nucleases as RNA-protein complexes offers a more favorable alternative by allowing transient expression and reducing unintended genome modifications. Engineered virus-like particles (eVLPs) have emerged as a promising appraoch, potentially replacing viral vectors as delivery vehicles under specific conditions.

VLPs, derived from various viral origins, can encapsulate gene editing nucleases by fusing with viral proteins. During the self-assembly of viral proteins, gene-editing nucleases can be incorporated into VLPs in the form of either RNA or proteins Researchers successfully installed a base editor within VLPs and delivered it *in vivo* to the liver of a mouse, achieving an editing efficiency of approximately 63% [34]. However, the efficacy of clinical-grade VLP protocols in HSPCs remains to be elucidated.

3.6. *in vivo* Targeting of HSPCs

HSPC gene editing is generally implemented through two primary approaches: *ex vivo* manipulation followed by transplantation or direct *in vivo* administration of editing vectors. In *ex vivo* autologous gene therapy, a patient's own HSPCs are mobilized and collected via apheresis, followed by gene editing in a controlled laboratory setting. The edited HSPCs are then reinfused into the patient. Following transplantation, patients undergo conditioning regimens involving chemotherapeutic or radiotherapy to eliminate existing cells and create space within the hematopoietic niche. However, in diseases requiring intensive conditioning, these regimens often cause severe adverse effects. Moreover, the patient-specific nature of autologous gene therapy result in high manufacturing costs, making *ex vivo* gene therapy financially inaccessible for many patients. To expand access to HSC gene therapy, an alternative approach involves non-invasively delivery of gene-editing tools directly to target cells or tissues *in vivo*. Current *in vivo* HSPCs delivery approaches predominantly utilize helper-dependent adenoviral vectors, necessitating prior HSPC mobilization to optimize transduction efficiency. Subsequently, low-dose chemotherapy is used to selectively edit these cells.

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Another *in vivo* gene delivery system involves cationic polymers, synthetic macromolecules with a positive charge that facilitate nucleic acid delivery. These polymers deliver large nucleic acids (e.g., plasmids, siRNA, mRNA) by forming nanosized polyplexes through electrostatic interactions, enabling transfection via endosomal escape [35]. Examples include DEAE-dextran and polyamino acids, which offer cargo size-independent complexation, simplified production, and optimized retention duration compared to viral vectors [36, 37]. However, their electrostatic assembly makes them highly sensitive to chemical environments, leading to chemical environments, leading to variable endocytosis and inconsistent endosomal escape efficiency [36]. Furthermore, the positive charge of cationic polymers can induce cytotoxicity by compromising membrane integrity. This inherent cytotoxicity can be mitigated through hydrophilic monomer incorporation (e.g., TEGMA), molecular weight optimization, and pKa modulation [38].

An alternative strategy for *in vivo* HSPC gene editing involves LNPs, lipid-based nanocarriers composed of four key components: ionizable cationic lipids (for efficient nucleic acid encapsulation and endosomal escape), cholesterol (for membrane stability), helper phospholipids (for structural stabilization and fluidity), and PEGylated lipids (to prevent aggregation) [39]. LNPs have several key advantages that enhance their suitability for *in vivo* gene-editing: Firstly, they protect nucleic acids from nuclease degradation, improving stability, shelf life, and bioavailability [40]. Secondly, advances in scalable microfluidic hybrid methods have simplified LNPs manufacturing, enabling large-scale production [41]. Thirdly, LNPs allow for repeated administration, making them particularly valuable for immunization and short-term treatment. Fourth, LNP-mediated gene editing achieves comparable levels of efficiency with one-third the required doses to other methods [42]. Lastly, RNP-encapsulated LNPs can be produced and transported in a lyophilized form, enhancing accessibility to treatment. Nevertheless, LNP-based delivery faces certain challenges. Traditional LNPs exhibit low tissue specificity outside the liver when administered intravenously, potentially limiting their therapeutic scope. However, direct injection of mRNA-LNPs into target organs has shown promise in addressing this limitation, with clinical trials already underway for direct mRNA-LNPs tumor injections. Additionally, transient mRNA-LNP systems are preferable to viral vectors with prolonged expression in slow-turnover tissues, as the "hit-and-run" mechanism ensures permanent genomic edits while reducing off-target mutations and immune responses.

A recent breakthrough demonstrated *in vivo* base editing of HSPCs via LNP-mediated delivery. Researchers successfully encapsulated mRNA encoding a base editor within LNPs and targeted the stem cell factor receptor CD117 in bone marrow HSCs. This lipid nanoparticle-based editing system enabled direct reprogramming of bone marrow stem cells *in vivo* without requiring donor cells or toxic conditioning regimens like chemotherapy or radiotherapy. The study achieved efficient HSCs editing under non-genotoxic conditions, offering a promising therapeutic approach for genetic disorders [43]. Another study highlighted an innovative LNP formulation with extended PEG-lipid alkyl chains (C18), which significantly improved nanoparticle delivery efficiency to the bone marrow following systemic administration. The refined formulation successfully delivered both short RNA (siCD45) and larger mRNA (Cre mRNA) payloads *in vivo* [44]. Furthermore, CD117 targeting has been demonstrated using a variety of ionizable lipid formulations.

Overall, *in vivo* gene editing targeting HSCs holds transformative potential for HSC gene therapy. However, significant advancements are required to achieve clinically viable efficacy.

4. Conclusion

HSPC gene editing holds transformative potential for treating genetic disorders, infectious diseases, and hematological conditions by enabling permanent correction of cellular functions. However, its clinical translation faces significant hurdles. At the laboratory stage, *ex vivo* approaches—reliant on costly and complex procedures like HSPC isolation, cytokine stimulation, and electroporation—limit

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accessibility and risk compromising cell viability. *in vivo* strategies, though promising for bypassing these barriers, struggle with inefficient targeting of HSPCs and risks such as off-target edits, p53-mediated DNA damage responses, and immunogenicity. Furthermore, safety concerns around double-strand breaks and the high costs of specialized manufacturing facilities underscore the need for safer, more scalable delivery systems.

To address these challenges, future efforts must prioritize the development of precision-targeted *in vivo* delivery platforms, such as lipid nanoparticles (LNPs), which offer advantages like repeatable dosing, reduced toxicity, and simplified production. Innovations in gene-editing tools (e.g., base editors to minimize DNA damage) and delivery technologies (e.g., engineered vectors for HSPC-specific homing) are critical to enhance specificity and safety. Simultaneously, streamlining manufacturing processes and reducing reliance on *ex vivo* infrastructure will improve cost-effectiveness and global accessibility. By integrating advances in biomaterials, computational biology, and immunology, the field can transition toward therapies that are not only curative but also equitable, ultimately revolutionizing the treatment landscape for diverse diseases.

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