Research on Treatment Strategies for the Treatment of Sicklemia Disease

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***Abstract*—Sickle Cell Disease (SCD) is one of the most common single-gene genetic diseases in the world, with high morbidity, high disability, and significant geographic and racial clustering. Currently, clinical treatment is based on symptomatic relief, and the traditional drug Hydroxyurea (HU) improves the condition by elevating fetal Hemoglobin (HbF), but there are long-term toxicity and efficacy limitations. This paper systematically comprehends the therapeutic progress of SCD through a literature review, focusing on the core strategies and research breakthroughs of gene editing technology. Studies have shown that the CRISPR/Cas9 system has realized the synergistic effect of pathogenic mutation correction and HbF induction in human cell models, which provides a new pathway for the eradication of SCD. However, the clinical translation of gene editing technology faces multiple challenges, including the off-target effect of CRISPR/Cas9, the insufficient editing efficiency of hematopoietic stem cells, the optimization of the safety of the delivery system, the development of novel mobilizing agents such as Plexafoc and chemically modified mRNA vectors, as well as the integration of new and emerging technologies, such as single-cell transcriptome sequencing.**

***Keywords*—Sickle Cell Disease (SCD), hydroxyurea, gene editing, targeted correction, Hemoglobin subunit *β*-Gene (HBB)**

I. Introduction

Sickle Cell Disease (SCD) is an autosomal dominant blood disorder caused by a mutation in the Hemoglobin *β*-chain gene (HBB gene GAG→GTG). When hemoglobin molecules are exposed to various environments, red blood cells and hemoglobin aggregate and deform to form a sickle shape [1]. Deformation allows red blood cells to pass from cell to cell, resulting in impaired nutrition of downstream tissues, which in turn leads to vascular obstruction, chronic hemolysis, and multi-organ damage. The clinical manifestations of patients are recurrent vaso-occlusive painful crises, chronic anemia, splenomegaly, stroke, acute chest syndrome, etc. In severe cases, it can involve vital organs such as the liver, kidneys, and lungs, causing irreversible damage. As one of the most common single-gene genetic diseases in the world, SCD has significant racial and geographic aggregation, mainly affecting populations in Africa, the Americas, the Middle East and the Mediterranean region [1].

According to the World Health Organization (WHO) in 2023, approximately 1.2 million newborns worldwide are born with SCD each year, of which more than 70% are born in sub-Saharan Africa. African countries such as Nigeria and the Democratic Republic of Congo (DRC) have neonatal prevalence rates as high as 1–2%, and the U.S. population of African descent carries the disease at a rate of about 8%, with more than 2000 new cases each year. The disease causes a serious health and socio-economic burden, with the highest mortality rate in childhood, and about 15–20% before the age of 5 in Africa [2]. Adults live an average of 20–30 years shorter than the healthy population and are dependent on blood transfusions, pain medications, and management of complications for long periods of time, resulting in high healthcare costs. However, 80% of patients worldwide still lack access to essential treatments, making SCD an urgent public health challenge. Although the pathomechanism of SCD is well defined, i.e., Hemoglobin S (HbS) aggregation leading to erythrocyte rigidity, available treatments are still focused on symptomatic relief, and there is a lack of curative therapies. The conventional drug Hydroxyurea (HU) improves the condition by boosting fetal Hemoglobin (HbF), but it has side effects such as bone marrow suppression. Hematopoietic Stem Cell Transplantation (HSCT) is a cure but is limited by the difficulty of matching and the risk of transplantation. In recent years, breakthroughs in gene-editing technology have brought hope for the eradication of SCD, especially the CRISPR-Cas9 system, which has shown remarkable potential in correcting disease-causing mutations and activating HbF expression.

This research focus on the therapeutic progress of SCD by means of a literature review, and analyze the mechanism of action, clinical efficacy, and application prospects of traditional drugs and emerging gene editing technologies, with the aim of providing a scientific basis for optimizing the therapeutic strategy.

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II. Treatment modalities

A. Hydroxyurea (HU)

1) Therapeutic mechanism

HU is a ribonucleotide reductase inhibitor that promotes the synthesis of HbF by inhibiting DNA synthesis and inducing erythroid precursor cell differentiation [3]. HbF forms a heterotetramer with HbS, which is used to reduce HbS aggregation and erythrocyte sickling, thereby reducing the incidence of Vaso-Occlusive Crisis (VOC) and concomitantly improving anemia. Mechanisms of action also include antioxidant effects, increased water content in erythrocytes to enhance deformability, and reduced adhesion of erythrocytes to endothelial cells [4]. Clinically, as a traditional pharmacological treatment, HU significantly reduces the frequency of pain episodes, prolongs crisis-free survival, and reduces the risk of acute chest syndrome and stroke in patients. Clinical trials have demonstrated that long-term use has the potential to improve chronic anemia in patients, thereby reducing the need for blood transfusions. The treatment is typically indicated for patients over the age of 5 with moderate-to-severe SCD, especially for those with more than three episodes of pain per year or a history of stroke [5]. In 2022, the FDA approved low-dose HU in combination with long-acting erythropoietin for pediatric patients. This expanded use further enhances the safety of the drug. According to NIH and WHO reports, HU is the recommended treatment for SCD globally, and its efficacy has been demonstrated in multicenter studies in Africa and the Americas [4]. The ACHIEVE-SCD clinical trial (NCT05451940) conducted in 2023 further explored the safety and efficacy of HU in combination with Erythropoietin (EPO) for the treatment of chronic anemia in SCD, and the results demonstrated that the modality significantly elevated hemoglobin levels, reduced the need for transfusions, and improved cardiac function markers [4]. In addition, HU can be used as an adjunct to gene editing therapy. For example, the use of HU to increase HbF levels before CRISPR-Cas9 treatment can enhance the anti-sickling ability of edited erythrocytes, and the combination of HU and crizanlizumab, a monoclonal antibody that targets selectins, can inhibit vascular occlusion and hemolysis at the same time, thus forming a "dual-pathway" intervention strategy [6].

2) Challenge

HU also has some shortcomings. HU treatment involves long-term medication, usually for more than 5 years. Secondly, it may cause side effects such as bone marrow suppression (neutropenia/thrombocytopenia), hair loss, and skin pigmentation. Prolonged use may cause problems such as skin cancer (e.g., squamous cell carcinoma), requiring patients to undergo regular skin examinations. For specific patients, such as HIV patients, it may increase the risk of hepatotoxicity when used in combination with antiretroviral medications. In addition, patients using HU treatment modalities need to be alerted to the risk of interstitial lung disease (including pulmonary fibrosis and alveolitis), requiring immediate discontinuation of the drug and treatment with glucocorticoids at the onset of respiratory symptoms. Approximately 20–30% of patients have been recorded as having a negative response to HU and remaining dependent on blood transfusions after treatment [5].

As the cornerstone of SCD treatment, HU can ameliorate the condition of SCD through multiple mechanisms, but the risk of toxicity in long-term use needs to be cautioned. In the future, it is necessary to further optimize the dosage regimen, explore combination therapy strategies, and improve accessibility in resource-limited areas to maximize its clinical value.

B. Gene Editing

Gene editing is a biotechnology cluster that precisely modifies specific DNA sequences of an organism's genome by artificial means, and its core goal is to regulate gene function in a targeted manner so as to achieve disease intervention, species improvement, or gene function resolution. The rise of third-generation gene editing tools, such as Zinc Finger Nucleases (ZFN), Transcription Activator-Like Effector Nucleases (TALEN), and CRISPR/Cas9 systems, has enabled the precise modification of genomic target sites, which has revolutionized the eradication of monogenic genetic diseases [7]. Thompson et al. and Biffi et al. successfully achieved the release of long-term blood transfusion dependence in 22 patients with β-thalassemia major by using the gene therapy protocol of transducing autologous CD34+ hematopoietic stem cells with BB305 lentiviral vectors, and no serious treatment-related adverse events were observed [8]. This fully demonstrated the clinical feasibility of gene-editing technology in hematologic diseases.

1) Therapeutic mechanism

As a typical single-gene dominant disease, the pathogenic mechanism of SCD is the GAG→GTG mutation in codon 6 of β-Hemoglobin Subunit Beta (HBB), which leads to erythrocyte sickling. Therefore, gene editing technology exerts therapeutic effects through two pathways, the first of which is pathogenic gene correction. zFNs, TALENs and CRISPR/Cas9 have successfully targeted and corrected the sickling process in human cells, altering and inducing HbF levels in clinically relevant cells [7]. HbF induction is an effective combination therapy for alleviating disease complications while correcting sickle cell mutations. The second pathway is γ-pearl protein gene activation, which enhances fetal hemoglobin (HbF, $\alpha 2\gamma 2$) levels through epigenetic modulation or sequence editing and utilizes the protective effect of HbF on sickle cell to alleviate clinical symptoms [9].

Studies have indicated that the combined application of mutation correction and HbF induction strategies can produce synergistic therapeutic effects [10]. To address the genetic heterogeneity of SCD, researchers constructed an induced Pluripotent Stem Cell (iPSC) library containing specific iPSCs with different ethnic backgrounds, HBB genotypes, and HbF levels, and optimized the CRISPR/Cas9 system to improve the efficiency of

mutation correction, which provided an ideal cell model for individualized therapy [10].

2) Issues and prospects

The off-target effect of the CRISPR/Cas9 system remains a key issue limiting its clinical application. Although the off-target risk has been significantly reduced by protein engineering modifications (e.g., Cas9 REC3 structural domain optimization), improved guide RNA (gRNA) design algorithms, and development of off-target monitoring techniques (e.g., Digenome-seq), more in-depth mechanistic studies are required to establish off-target editing systems [11]. In Homologous Recombination Repair (HDR)-based precision editing, the editing efficiency of primitive reconstructed hematopoietic stem cells was lower, and the gene modification level of mature hematopoietic stem cells was significantly higher than that of immature cells. In HDR-based gene editing, transient overexpression of BCL-2 mRNA preserved hematopoietic stem cell activity and increased the frequency of gene-corrected hematopoietic stem cells [12].

In addition, the conventional mobilizing agent Granulocyte Colony-Stimulating Factor (G-CSF) may induce vaso-occlusive crisis in SCD patients due to activation of the coagulation system and neutrophils. The novel CXCR4 inhibitor Plexafoc (plerixafor) achieves efficient hematopoietic stem cell mobilization without complications by blocking the CXCL12/CXCR4 signaling axis, which opens a safe pathway for cell acquisition for gene editing therapy [13].

Furthermore, to address the shortcomings of conventional mRNA vectors, which are highly immunogenic and unstable, chemical modification techniques (e.g., nucleoside analog substitution) can reduce Toll-Like Receptor (TLR) recognition and increase the protein expression efficiency of mRNAs in vitro and in vivo by 5-10-fold [14]. Such modified mRNA vectors have demonstrated the potential to precisely regulate HbF expression in the delivery of gene editing tools (e.g., Cas9 proteins) and have emerged as candidates for SCD therapy [14].

Since gene editing technologies have been effective in correcting SCD cell phenotypes in in vitro models, the central goal of clinical translation is to balance editing efficiency and safety. Emerging technologies such as single-cell Transcriptome-sequencing (scRNA-seq) can accurately resolve the gene expression profiles of edited cell subpopulations, providing a molecular basis for optimizing therapeutic regimens at the single-cell level [9]. With the maturation of new generation technologies such as base editing and prime editing, the curative treatment of SCD is expected to move from the laboratory to the clinic, setting a model for precision medicine for monogenic genetic diseases.

III. Conclusion

As a global, highly prevalent monogenic genetic disease, the prevention and treatment of SCD face serious clinical and public health challenges. Although the traditional drug HU, which improves symptoms by elevating HbF levels, is the primary therapeutic option, its long-term toxicity, insufficient response for some patients, and limitation of symptomatic relief have prompted the medical community to accelerate the search for curative therapies. The rise of gene-editing technology has created a breakthrough in the treatment of SCD. Through the dual strategy of pathogenic gene correction and γ-pearl protein gene activation, it has demonstrated the potential of correcting pathogenic mutations and restoring normal erythrocyte function in in vitro models and preclinical studies.

However, the clinical translation of gene editing technology still faces multiple challenges. The off-target effect of the CRISPR/Cas9 system, the insufficient editing efficiency of hematopoietic stem cells, and the optimization of the safety of the delivery system need to be solved urgently. Meanwhile, the research and development of new mobilizing agent Plexafoc and chemically modified mRNA carriers provide new ideas to break through the bottleneck of traditional technology. In the future, it is necessary to integrate emerging technologies such as single-cell transcriptome sequencing to accurately analyze the functional characteristics of edited cells at the molecular level, and to combine the technological advantages of new-generation tools such as base editing and leading to building an efficient and safe individualized treatment system.

It is also worth noting that the prevention and treatment of SCD should be balanced between technological innovation and medical accessibility.

While gene editing technology is moving towards the clinic, it is still necessary to optimize the combination of hydroxyurea, enhance its popularity in resource-limited areas, and form a stepwise treatment strategy of "symptomatic relief-genetic cure". With the deep integration of basic research and translational medicine, SCD is expected to become the first single-gene genetic disease to be eradicated on a large scale by gene-editing technology, providing a paradigm reference for the treatment of rare diseases around the world.

Conflict of Interest

The authors declare no conflict of interest.

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