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Current status and perspectives of gene therapy in the treatment of haematological cancers

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Abstract. Gene therapy holds great promise in the treatment of haematological cancers. Haematological cancers account for a significant portion of cancer cases worldwide, making gene therapy research in this area crucial. The emergence of breakthrough technologies, especially CRISPR-based gene editing, has enriched gene therapy possibilities and ushered in new opportunities for cancer treatment. Despite the potential benefits, gene therapy faces challenges related to safety and technical advancements. This work discusses practical applications of gene therapy, such as the use of monoclonal antibodies and gene transfer in haematological tumour cells. It also highlights the prospects of CRISPR gene editing technology, which has gained momentum in clinical applications for cancer treatment. However, it acknowledges potential risks and limitations, such as off-target effects and unpredictable translational outcomes. The conclusion emphasizes the need for further research to enhance long-term effectiveness, safety, and accessibility of gene therapy, using human genome sequencing, improved delivery technology, and better understanding of disease genes and biological mechanisms.

Keywords: Haematological Cancer, Gene Therapy, CRISPR.

1. Introduction

Haematological cancers include various diseases (Hodgkin's lymphoma, non-Hodgkin's lymphoma, leukaemia and multiple myeloma. The incidence rate of haematological malignancies accounts for the 6th place in the overall incidence rate of cancer in the world; the mortality rate of patients with haematological malignancies from 0 to 15 years of age ranks the first in the total mortality rate of cancer; the mortality rate of male patients with haematological malignancies from 15 to 34 years of age is second only to other non-disease-related deaths; the mortality rate of female patients with haematological malignancies is second only to that of breast cancer; and the incidence of haematological malignancies of males over 55 years of age and females over 75 years of age is significantly increased [1].

Gene therapy is a therapeutic means to treat diseases by modifying or manipulating the expression of genes to change the biological properties of living cells. In particular, the continuous emergence of breakthrough technologies such as CRISPR has further enriched the gene therapy technology system and brought new opportunities for the development of gene therapy. At present, more than 10 gene therapy products have been marketed globally, especially in 2022, 4 products will be the first in the world, and all of them are the first gene therapy drugs for the corresponding indications. CRISPR-

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based gene editing therapies are also entering the stage of marketing application in 2022 [2]. As gene therapy can effectively regulate gene expression or correct gene mutations, it is of great research and clinical application value for the treatment of cancer.

2. Literature Review

Since the discovery of gene therapy technology, many researchers and institutions have been actively exploring its application in haematological tumour therapy. Early studies focused on gene knockout, gene repair and gene addition to verify the feasibility and effectiveness of gene therapy technology. With the maturity and development of the technology, more and more studies have begun to focus on the precise positioning and personalised treatment of gene therapy technology in haematological tumour therapy. These studies have demonstrated many potential applications of gene therapy technology in haematological tumour therapy. Some studies have shown that through gene editing, genes associated with haematological tumours can be targeted to be suppressed or repaired, thus enabling precise treatment. In addition, gene therapy techniques have been used to enhance the effectiveness of immune cell therapy by improving their ability to recognise and attack tumours. These studies provide valuable references for further development of haematological tumour treatment strategies.

Although gene therapy technology shows great potential in haematological tumour therapy, there are still some problems and challenges. Firstly, the safety of gene therapy technology is an important concern, as gene editing may lead to non-specific side effects or potential adverse reactions. In addition, there are still many technical, regulatory and ethical challenges to be faced in order to effectively translate gene therapy technology into clinical practice.

3. Practical application of gene therapy in the treatment of haematological tumours and prospects for clinical application

3.1. Practical application

Monoclonal antibodies and their coupled specificity-directed therapies involve the use of monoclonal antibodies specific for anti-tumour cells as carriers in combination with cytotoxic substances such as radioisotopes, chemotherapeutic drugs, toxins, etc., which are directed to or brought to the site of the tumour to destroy the tumour cells. In recent years, mouse-derived monoclonal antibodies have been humanised to make them easy to apply in vivo. With the development of genetically engineered antibodies such as chimeric antibodies and single-chain antibodies, they have shown good application prospects. The tyrosine kinase encoded by oncogene Bcr/Abl plays a key role in the pathogenesis of chronic myelogenous leukemia (CML), and the newly researched STI 571 (Gleevec) is a specific inhibitor against the phosphorylation of this tyrosine kinase, which is not only effective against "CML" chronic phase, but also effective in the acute phase of CML. Anti-CD33 monoclonal antibody has achieved some efficacy in the treatment of acute non-lymphocytic leukemia (ANLL; or acute myeloid leukemia, AML) in children; anti-CD20 antibody (Merovia) has been successfully used in the treatment of lymphoma; anti-CD19, anti-CD22, anti CD19, anti-CD22, anti-CD52, anti-CD25 and anti-CD45 antibodies have been successfully developed one after another, creating a new era for haematological tumour-directed therapy. The pathogenesis of multiple myeloma is closely related to bone marrow stromal cells and cytokines, and the application of anti-IL-6 antibody and PS-341 (to inhibit the secretion of cytokines by stromal cells and tumour cells) has obtained encouraging results [3].

Haematological cancers are a group of diseases with genetic abnormalities for which gene therapy provides a highly specific treatment. The application of marker genes can more accurately grasp the information about the presence, distribution, and activity of tumour-specific killer cells in the body after patients receive immunotherapy. The transfer of multiple drug resistance gene-1 (MDR1) into normal haematopoietic stem cells can increase the dosage of the relevant cytotoxic drugs, thus prolonging the duration of drug administration. The introduction of genes encoding certain cytokines,

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lymphokines and co-stimulatory molecules into haematological tumour cells, such as acute lymphoblastic leukemia (ALL) , AML, CML, and chronic lymphocytic leukemia (CLL), and transfuse into patients can increase the dose of relevant cytotoxic drugs, thus prolonging the duration of drug administration and improving the cure rate. , CLL) and infused back into the patient, can stimulate anti-tumour effects in non-genetically transferred tumour cells expressing the same specific antigen elsewhere in the body [4].

3.2. Prospects for clinical application

Back in 2016, CRISPR-Cas9 gene editing technology achieved its first clinical application in oncology therapy, transplanting gene-edited immune cells to a patient with advanced lung cancer [5]. 2020 saw the birth of a technology called very fast CRISPR (vfCRISPR), which is capable of sub-micrometre and sub-second DSBs, fuelling the study of high-precision DNA repair in space, time and genomic coordinates [6]. Currently, CRISPR-Cas9 technology has been approved by the National Institutes of Health (NIH) Recombinant DNA Advisory Committee to enter clinical trials in the United States [7]. The committee allowed the recruitment of patients through the NIH for T-cell assisted cancer therapy using CRISPR technology [8]. Similar gene therapy clinical trials have received ethical approval in China [9]. The conduct of a large number of clinical trials is expected to establish an effective therapeutic genome editing system for human malignancies. Therefore, CRISPR gene editing technology is full of prospects for clinical treatment, especially cancer treatment.

4. Potential risks and security issues

Gene therapy has been a popular new track in today's life sciences, and the most representative CRISPR system, as a gene editing tool, has revolutionised the life sciences and provided new powerful tools for biological systems and human disease research. The application potential of CRISPR-Cas9 gene editing technology has gradually emerged in the fields of basic and translational medical research on tumour, such as tumour mechanism research, drug target screening and clinical treatment [10], but there are certain limitations.

First, off-target effects are common in human cell cultures that consistently express Cas9 [11], but this is less common in in vivo models. The high off-target effect in cell cultures may be influenced by the variability of multiple factors, such as cell type, expression level, transfection method, cell culture maintenance, continuous nuclease expression, bootstrap sequences, and repair events. Off-target effects are mainly caused by sgRNAs, therefore, the rational design of sgRNAs is crucial for the effectiveness of CRISPR-Cas9 gene editing technology. sgRNA-induced double-strand breaks (DSBs) followed by repair mechanisms or genome rearrangements are also risk points in CRISPR-Cas9 therapeutic interventions. Although CRISPR-Cas9 technology can induce targeted mutations in genomic sequences, we know little about the DNA repair mechanisms and have limited control methods. The repair modes of DSBs include non-homologous end joining (NHEJ) and homology-directed repair (HDR), the former is error-prone and may lead to mutations, while the latter is more precise but has a very low incidence [12]. Therefore, when implementing CRISPR-Cas treatment protocols, improving HDR effectiveness and reducing NHEJ are key to repair to ensure that gene editing achieves the desired results.

Second, the clinical translational outcomes of CRISPR-Cas9 gene editing systems are unpredictable [13]. The main reasons for this are 1) insufficient analysis of experimental data; and 2) the very limited number of cell types suitable for in vitro editing as most highly differentiated cells after mitosis can only function in vivo [14]. Therefore, these limitations need to be considered in depth before entering clinical use.

With the advancement of genome editing technology, genome editing studies related to CRISPR-Cas9 for the treatment of human diseases are rapidly developing. However, the application of CRISPR-Cas9 to patients with serious life-threatening diseases is still an emerging technology, and most clinical trials are only in phase I/II. To date, clinical trials have focused on the safety and efficacy of human genome editing to improve the molecular processes involved in genome editing. The ethical

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controversy over the application of therapeutic gene editing techniques in the early human embryo genome is changing, suggesting that the scientific community is establishing gene editing regulations. In conclusion, CRISPR-Cas9 offers a completely new perspective on the treatment of deadly human diseases.

5. Conclusion

Over the past decade, gene therapy has made a number of breakthroughs, and in the future, further enhancing long-term effectiveness and safety as well as improving accessibility will become the focus of gene therapy development.

From a research perspective, in the era of big data, making full use of the results of human genome sequencing, strengthening basic research on diseases, and developing more new targets, mechanisms and treatments will greatly break through the current gene therapy methods. As the key technology in gene therapy process, the progress of delivery technology will greatly promote the application scope of gene therapy, and new gene therapy vectors with high efficiency, safety and low immunogenicity still need to be optimised and developed.

In addition, the field of gene therapy should also pay attention to the durability and safety of treatment and accessibility. At present, the durability of gene therapy still needs to be proved by long-term follow-up. In terms of safety, human beings currently have limited understanding of the function of disease genes and related biological mechanisms, making gene therapy still face certain risks. Enhancing the biological understanding of diseases will improve the safety of gene therapy, and at the same time, improving the editing efficiency will also reduce the unknown safety problems caused by the off-target effect of gene editing technology. Overall, long-term, comprehensive and in-depth preclinical and clinical studies are needed to ensure the safety and effectiveness of gene therapy. In terms of drug accessibility, gene therapy drugs firmly occupy the list of the world's most expensive drugs, and in the future, it may be possible to further reduce production costs through key technological innovation, optimisation of production technology, etc., as well as exploring new payment conditions and health insurance conditions, such as instalment payment and payment according to the efficacy of the treatment.

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