MedSci Publisher®
International Journal of Molecular Medical Science, 2023, Vol.13, No.2, 1-7
http://medscipublisher.com/index.php/ijmms

Review and Progress Open Access

Theoretical and Historical Development of Gene Editing and Gene Therapy

Wang Wei
Cuixi Academy of Biotechnology, Zhuji, 311800, China
Corresponding author email: 2741098603@qq.com
International Journal of Molecular Medical Science, 2023, Vol.13, No.2 doi: 10.5376/ijmms.2023.13.0002
Received: 07 Sep., 2023
Accepted: 15 Sep., 2023
Published: 22 Sep., 2023

Preferred citation for this article:
Wang W., 2023, Theoretical and historical development of gene editing and gene therapy, International Journal of Molecular Medical Science, 13(2): 1-7 (doi: 10.5376/ijmms.2023.13.0002)

Abstract Gene editing and gene therapy have been the forefront technologies in life sciences that have received increasing attention in recent years. They provide new avenues and methods for the treatment of human diseases and biological research. This review systematically elucidates the concepts and historical developments of gene editing and gene therapy. It introduces the definition, classification, technical principles, and application areas of gene editing, and reviews the origin, development, and commercialization of gene editing technologies. The definition, classification, technical principles, and application areas of gene therapy are analyzed, and the origin, development, and clinical application status of gene therapy technologies are discussed. Furthermore, the significance, prospects, challenges, and future directions of gene editing and gene therapy are explored. This review provides references and insights for a comprehensive understanding of gene editing and gene therapy, and scientific basis for advancing the application and development of gene editing and gene therapy in the field of biomedical research.
Keywords Gene editing; Gene therapy; Technological origins; Fundamental concepts; Historical development

With the continuous development of life science and technology, gene editing and gene therapy as two advanced technologies are gradually becoming the focus of attention. Gene editing and gene therapy are two emerging life science technologies that can be used to decipher the code of the human genome and alter the destiny of human health and disease. In recent years, with the ongoing development and improvement of gene editing and gene therapy technologies, their applications and research in the field of biomedicine have become increasingly extensive and in-depth.

Gene editing technology is a technique that enables precise editing and regulation of the genome, and it has become a hot research area in the fields of life science and medicine. Gene editing technology can be applied to the treatment and prevention of various diseases, such as monogenetic disorders, cancer, and immune deficiencies. It can also be applied in precision medicine, agriculture, and biotechnology. Its development will bring more opportunities and challenges to gene function research, disease treatment, and biotechnology. The research on gene editing technology began in the 1980s, and the earliest gene editing technique was achieved using zinc finger nucleases (ZFNs) to edit and regulate the genome. With further research, more efficient, precise, and user-friendly gene editing technologies such as TALENs and CRISPR/Cas9 have emerged. These technologies have expanded the application of gene editing and provided researchers with more tools and means.

Gene therapy is an emerging therapeutic approach that involves the introduction of normal genes into the body to repair or replace defective genes, thereby achieving the goal of treating diseases. Gene therapy can be applied to the treatment and prevention of various diseases, such as monogenetic disorders, cancer, and immune deficiencies. Compared to traditional drug therapy and surgical treatment, gene therapy has the characteristics of being more precise, personalized, and long-lasting. Currently, gene therapy has been proven to play an important role in the treatment of some diseases. For example, gene therapy has been successfully used to treat severe immune deficiencies, cystic fibrosis, and holds promise in the fields of cancer, cardiovascular diseases, and neurological disorders.

Both gene editing and gene therapy have been widely applied in biological research and have brought new ideas and hopes for the treatment of human diseases. This review aims to provide a comprehensive overview of the concepts and historical developments of gene editing and gene therapy. It introduces the definitions, classifications, technical principles, application areas, historical developments, and future prospects of these two technologies, as well as discusses the ethical and legal issues they face. Through the exposition in this review, readers are expected to gain a deep understanding of the principles, features, and applications of gene editing and gene therapy, as well as grasp the historical development and current status, providing valuable references and insights for their application and development in the field of biomedicine.

1 Concept and Principles of Gene Editing

1.1 Definition and classification of gene editing

Gene editing refers to the modification and editing of DNA sequences in cells or organisms through specific technical approaches, thereby generating specific gene expression patterns and products (Lu et al., 2018). The development of gene editing technology has advanced the study of gene function and gene regulatory mechanisms, while also providing new ideas and methods for disease treatment and agricultural production.

Gene editing technologies can be classified into CRISPR/Cas9, TALEN, ZFN, and RNA-based editing technologies, based on different editing methods. The above-mentioned gene editing technologies enable precise regulation and alteration of the genome, and find applications in gene function research, disease model construction, gene therapy, and more. With the continuous development and improvement of gene editing technologies, their applications and research in the biomedical field are becoming increasingly widespread and in-depth.

1.2 Gene editing principles and common methods

The principle of gene editing technology involves cutting, modifying, inserting, or deleting DNA molecules within cells or organisms to achieve precise regulation and alteration of the genome. Common methods of gene editing technology include CRISPR/Cas9, TALEN, ZFN, etc.

CRISPR/Cas9 technology is an emerging gene editing technique (Figure 1), based on the CRISPR/Cas system derived from a bacterial immune system. It involves the introduction of Cas9 protein and corresponding guide RNA (gRNA) to specific gene loci for DNA double-strand cleavage and repair, thereby enabling gene modification, insertion, deletion, etc. (Yang et al., 2019). The main steps of CRISPR/Cas9 technology include designing and synthesizing gRNA, introducing Cas9 protein and gRNA into cells, targeting specific gene loci for DNA double-strand cleavage, and repairing DNA breaks, thus achieving precise regulation and alteration of the genome.

TALEN technology is an artificial restriction enzyme technology based on transcription activator-like effectors (TALEs). TALEN technology involves designing and synthesizing TALEN proteins that target specific gene loci for DNA double-strand cleavage and repair (Song et al., 2021). The main steps of TALEN technology include designing and synthesizing TALEN proteins, introducing TALEN proteins into cells, targeting specific gene loci for DNA double-strand cleavage, and repairing DNA breaks, thereby achieving precise regulation and alteration of the genome.

ZFN technology is an artificial restriction enzyme technology based on zinc finger proteins. It involves designing and synthesizing specific ZFN proteins that target particular gene loci for DNA double-strand cleavage and repair. The main steps of ZFN technology include designing and synthesizing ZFN proteins, introducing ZFN proteins into cells, targeting specific gene loci for DNA double-strand cleavage, and repairing DNA breaks to achieve precise regulation and alteration of the genome.

In addition, RNA-based editing technologies are also common gene editing methods, including RNA editing and RNA interference. These techniques involve editing or interfering with RNA sequences to achieve gene regulation and therapy. In summary, gene editing technologies enable precise regulation and alteration of the genome by cutting, modifying, inserting, or deleting DNA molecules within cells or organisms. With the continuous development and improvement of these technologies, the applications and research of gene editing are becoming increasingly widespread and in-depth.

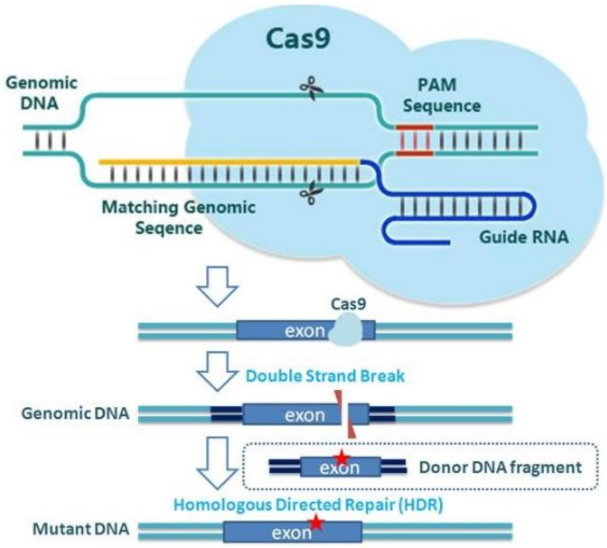

Figure 1 Working principle of CRISPR/Cas9 technology

1.3 Applications of gene editing in medical research

Gene editing technology can be used in various aspects of medical research, including gene function studies, disease modeling, and gene therapy. Here are some applications of gene editing in medical research. Firstly, disease modeling: Gene editing techniques can be utilized to create disease models to investigate disease mechanisms and treatment strategies. For instance, scientists have employed CRISPR/Cas9 technology to generate models of human genetic diseases such as cystic fibrosis and amyotrophic lateral sclerosis in mice and monkeys. Secondly, gene function studies: Gene editing technology can be employed to study gene functions and regulatory mechanisms. Scientists can study the roles of specific genes in cell growth, differentiation, and function by deleting or modifying them. Gene editing technology can also be applied in gene therapy, where it is used to treat certain genetic diseases, such as cystic fibrosis and hereditary blindness (Niu et al., 2019). Scientists can repair or replace defective genes using gene editing techniques, restoring normal cellular functions. This approach is known as gene therapy. Gene editing technology can be used in the treatment of certain types of tumors as well. For example, scientists can enhance the immune cells' ability to attack tumors using gene editing techniques, leading to the therapeutic effect in tumor treatment.

In summary, gene editing technology has extensive applications in medical research, enabling scientists to better understand the mechanisms of disease occurrence and development. It also provides new insights and methods for disease treatment and prevention. With the continuous development and improvement of the technology, the application and research of gene editing will continue to deepen and expand.

2 Historical Development of Gene Editing

2.1 Origins and development of gene editing technology

The origin of gene editing technology can be traced back to the 1970s when scientists invented a genetic scissor that could cut DNA molecules. This genetic scissor is known as a restriction enzyme, capable of cleaving DNA into specific fragments, enabling the construction of gene libraries and the study of gene function and structure. With technological advancements, gene editing techniques have gradually been improved and refined. In the 1990s, scientists developed a novel gene editing technology called transgenic technology, which allows the introduction of foreign genes into cells or organisms, thereby altering their gene expression patterns and products.

However, transgenic technology has many challenges, such as low efficiency and difficulty in precise control. To address these issues, scientists began exploring the use of artificial nucleases for gene editing in the late 20th century. These artificial nucleases can be designed and synthesized to possess precise DNA recognition and cleavage capabilities. In the early 21st century, scientists successfully achieved gene editing using artificial nucleases like zinc finger proteins and transcription activator-like effector nucleases (TALENs). However, these techniques still had limitations, such as low efficiency and difficulties in design and synthesis (Li et al., 2022). It was not until 2012 when scientists invented a new gene editing technology known as CRISPR/Cas9. CRISPR/Cas9 technology offers advantages such as high efficiency, precision, and ease of use, and has become one of the most commonly used gene editing techniques today.

In summary, after years of development and improvement, gene editing technology has become a crucial tool for studying gene functions and regulatory mechanisms, as well as for the development of gene therapy and bioproducts. With the continuous advancement of technology, we believe that the application and research of gene editing will continue to deepen and expand.

2.2 Breakthroughs and Advances in Gene Editing Technology

After years of development and improvement, gene editing technology has achieved a series of breakthroughs and advancements in various fields, including scientific research and medical applications. The progress in the invention and application of CRISPR/Cas9 technology (Figure 1) stands out. CRISPR/Cas9 is an efficient, precise, and easy-to-use gene editing technology that enables precise regulation and alteration of the genome. Its invention and application are considered a major breakthrough in gene editing technology and have been widely used in gene function research, disease model construction, gene therapy, and more.

In the field of gene therapy, gene editing technology has provided new ideas and methods. In recent years, gene editing technology has achieved some success in the treatment of genetic diseases such as cystic fibrosis, genetic blindness, and more. Additionally, gene editing technology is also being researched in the field of cancer therapy, offering new hope for treating certain refractory diseases.Genome editing breakthroughs have been made as well. In recent years, scientists have utilized gene editing technology to manipulate the human genome, exploring its functions and regulatory mechanisms. For instance, in 2015, researchers successfully edited the human embryo genome using CRISPR/Cas9 technology, opening up new avenues and methods for human genome editing research.In terms of improving gene editing technology, besides CRISPR/Cas9, many other gene editing technologies are continuously being developed and refined. Scientists are researching to enhance the efficiency and precision of techniques such as TALENs and ZFNs.

3 Concepts and Principles of Gene Therapy

3.1 Definition and classification of gene therapy

Gene therapy is a method that utilizes genetic engineering techniques to treat diseases. It aims to correct or prevent specific diseases by modifying the patient's genes. Gene therapy involves introducing healthy genes into the patient's body to repair or replace abnormal genes or regulate gene activity. Gene therapy can be classified into several main categories: gene replacement therapy, gene editing therapy, gene addition therapy, RNA interference therapy, and immune gene therapy. These classifications represent some common methods of gene therapy, but in practice, a combination of various techniques and approaches may be used to achieve therapeutic goals. Currently, gene therapy is still in the research and development stage, but it holds tremendous potential and may provide new hope for the treatment of many rare and genetic diseases.

3.2 Technical principles and common methods of gene therapy

The technical principle of gene therapy is to introduce a normal gene sequence into the patient's cells or tissues to replace defective genes or alter gene expression patterns, thereby achieving therapeutic effects. Common methods of gene therapy include gene replacement therapy, gene editing therapy, gene addition therapy, and RNA interference therapy.Gene replacement therapy involves introducing a normal gene sequence into the patient's cells or tissues to replace defective genes. This method usually utilizes vectors to deliver the normal gene into the patient's body. Common vectors include viruses and plasmids.Gene editing therapy aims to treat diseases by directly editing the genes within the patient's body. Common gene editing techniques include CRISPR/Cas9, TALENs, and ZFNs. These technologies enable the specific editing of the patient's target gene sequence to correct defective genes or alter gene expression patterns.Gene addition therapy involves adding new genes into the patient's cells or tissues to treat diseases. This method typically uses vectors to introduce the new gene into the patient's body, enabling its expression within the cells. Gene addition therapy is commonly used in cancer treatment, such as CAR-T cell therapy.RNA interference therapy (Shi and Jin, 2008) suppresses or targets specific genes by introducing RNA interference molecules to treat diseases. RNA interference molecules can be delivered into the patient's body through vectors such as plasmids or viruses to inhibit or reduce the expression of specific genes.

3.3 Applications of gene therapy in clinical medicine

Gene therapy holds the potential to treat diseases by modifying or repairing genes within the patient's body. Currently, gene therapy has found application in several fields of clinical medicine, including the treatment of genetic diseases, cancer, immune system disorders, and cardiovascular diseases. Gene therapy has been used to treat certain genetic diseases, such as cystic fibrosis and inherited blindness (Li and Chen, 2020). For example, in 2019, a gene therapy drug was approved by the European Union for the treatment of a rare genetic disease known as fatty acid acyl-CoA dehydrogenase (LCAD) deficiency. Gene therapy has also been employed in the treatment of certain types of cancer. For instance, some gene therapy drugs have been approved for the treatment of specific cancers, such as CAR-T cell therapy (Figure 2). Additionally, gene therapy can enhance the efficacy and reduce side effects by targeting cancer-specific genes. Furthermore, gene therapy has been used in the treatment of immune system disorders, such as rheumatoid arthritis and inflammatory bowel disease. For instance, some gene therapy drugs have been approved for the treatment of rheumatoid arthritis.Gene therapy has also been utilized in the treatment of certain cardiovascular diseases, including heart failure and coronary heart disease. For example, some gene therapy drugs have been used in the treatment of heart failure (Deng, 2005).

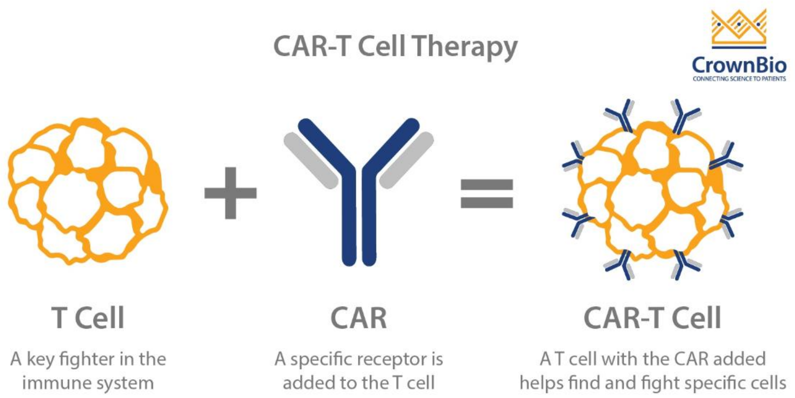

Figure 2 CAR-T cell therapy

4 History and Development of Gene Therapy

4.1 Origins and development of gene therapy technology

The origins of gene therapy technology can be traced back to the 1960s when scientists first attempted to use DNA molecules for the treatment of genetic diseases. The earliest gene therapy experiments were conducted in the 1970s, when scientists attempted to deliver normal genes into human cells using viruses in cell culture, and then transplanting these cells into patients. However, these experiments did not yield significant therapeutic effects, and safety concerns arose, leading to a temporary halt in the development of gene therapy.

It was not until the 1990s that gene therapy technology regained momentum with the rapid development of genetic engineering and biotechnology. In the early 1990s, scientists discovered that viruses could be used as vectors (also known as "gene delivery systems") to introduce normal genes into patient cells, thereby repairing or replacing defective genes (Mao, 2010). Subsequently, some gene therapy trials began to be conducted in clinical settings and achieved some initial successes. With continuous technological advancements, gene therapy has been extensively researched and applied. Currently, it has been used to treat some rare genetic diseases, cancers, and other diseases, and it continues to evolve and improve.

4.2 Breakthroughs and advances in gene therapy technology

In recent years, gene therapy technology has achieved significant breakthroughs and advances, including the development of gene editing technologies, improvement of gene delivery systems, the approval of gene therapy drugs, and the expanding clinical applications of gene therapy. CRISPR-Cas9 is a gene editing technology that enables precise editing of gene sequences. Its invention and development have made it easier for scientists to manipulate genes for the treatment of various diseases. Additionally, other gene editing technologies such as TALEN and ZFN have also emerged. Gene delivery systems are vehicles used to introduce therapeutic genes into the patient's body. Many new gene delivery systems have been developed, including liposomes, polymers, and metal-organic frameworks, which improve the efficiency and safety of gene delivery. Several gene therapy drugs have already been approved, such as Luxturna by Spark Therapeutics for the treatment of a rare inherited eye disease, as well as Kymriah by Novartis and Yescarta by Gilead Sciences for certain types of cancer. Currently, gene therapy is being used to treat some genetic diseases, cancers, immune system disorders, and cardiovascular diseases, with its clinical applications continuously expanding. Moreover, there are ongoing research studies on new gene therapy approaches, such as gene editing and CAR-T cell therapy.

In summary, gene therapy technology has made significant advancements in both technical development and clinical applications. With continuous improvement, gene therapy holds the promise of becoming one of the crucial strategies for treating various diseases in the future.

5 Conclusion and Outlook

Gene editing and gene therapy are two distinct yet related technologies that can be used for treating various diseases. Gene editing technology enables precise modification of gene sequences to repair or correct defective genes, while gene therapy involves the introduction of normal genes to repair or replace defective ones. Both these technologies have broad applications and hold great potential for treating a wide range of genetic diseases, cancers, immune system disorders, cardiovascular diseases, and so on.

With the continuous advancement of technology and the expanding applications, the clinical prospects of gene editing and gene therapy are becoming increasingly promising. Currently, there are already approved gene therapy drugs on the market for treating certain diseases, such as Luxturna, Kymriah, and Yescarta. Additionally, there are ongoing research studies on new gene therapy approaches, such as gene editing and CAR-T cell therapy. The continuous development and improvement of these technologies will greatly facilitate the application and advancement of gene therapy.

While gene editing and gene therapy technologies have made some progress in clinical applications, further research and improvement are still needed to enhance their safety and stability. In terms of gene editing, there is a need for continued research to address issues related to precision and safety, ensuring stability and safety in clinical applications. In the domain of gene therapy, further research is required to address challenges associated with gene delivery systems to improve the efficiency and safety of gene delivery.

In addition, the application of gene therapy technology also faces many ethical and societal issues (Yang et al., 2013). For example, questions arise regarding how to protect patients' right to privacy and right to know, as well as ensuring fairness and accessibility in gene therapy. Therefore, while promoting the advancement of gene therapy technology, it is crucial to strengthen research and address ethical and societal concerns to ensure fairness and sustainability in its clinical applications.

In summary, gene editing and gene therapy technologies are important directions for future developments in the field of medicine. While there are still various technical and ethical issues that need to be addressed, with the continuous improvement of technology and the expansion of applications, gene therapy holds the potential to become a significant strategy for treating various diseases.

Authors' contributions

WW was the primary writer of the review, responsible for collecting and analyzing relevant literature, as well as writing the initial draft of the paper. WW also participated in the analysis and organization of the literature. I have read and approved the final manuscript.

Acknowledgments

I would like to express my gratitude to Ms. Xuan Jia for reviewing this review and providing valuable feedback for the paper. The images used in this review are obtained from the internet, and I acknowledge and respect the rights of each image owner. If any copyright violations are identified with the images, please feel free to contact the author at any time.

References

Deng H.X., Tian L., and Wei Y.Q., 2005, Current status, problems and prospects in gene therapy, Shengming Kexue (Chinese Bulletin of Life Sciences), 20(2):196-201.

Li L., Zhu X.M., Bao J.D., Wang J.Y., and Lin F.C., 2022, Gene editing:past and present, Zhejiang Nongye Xuebao (Acta Agriculturae Zhejiangensis), (5): 1091-1102.

Li W.S., and Chen X.D., 2020, Current status and challenges of the gene therapy clinical trials for hereditary retinal diseases, Yanke (Ophthalmology in China), 29(4): 241-245.

Lu J.N., Chu X., Pan Y.P., Chen Y.X., Wen L., and Dai J.B., 2018, Advances and Challenges in Gene Editing Technologies, Zhonguo Kexueyuan Yuankan (Bulletin of Chinese Academy of Sciences), 33(11): 1184-1192.

Mao J.P., 2010, The 20 years of gene therapy, Zhonguo Shengwu Gongcheng Zazhi (China Biotechnology), 30(9): 124-129.

Niu X.R., Yin S.M., Chen X., Shao T.T., Li D.L., 2019, Gene editing technology and its recent progress in disease therapy, Hereditas (Beijing), 41(7): 582-598.

Shi Y., and Jin Y.X., Advances in the research of RNAi and siRNA, Shengming Kexue (Chinese Bulletin of Life Sciences), 20(2): 196-201.

Song S.Z., Zhang T., Lu R., Cheng Y., and Zhou M.M., Research progress in application of TALEN and CRISPR/Cas9, two major instruments for the "Humanization" of goat milk, Jiyin Zuxue Yu Yingyong Shengwuxue (Genomics and Applied Biology), 40(4): 1584-1589.

Yang C., Guo X., and Xie J., 2013, Ethical discussion on gene therapy technology, Zhonguo Yixue Lunlixue (Chinese Medical Ethics), 26(3):331-333.

Yang C.Y., Wang L., Mu D.C., Li F.F., Shen H., and Zheng S.Y., 2019, Advances of Gene Editing in Disease Treatment, Zhonguo Shengwu Gongcheng Zazhi (China Biotechnology), 39(11): 87-95.