Recent Advances in CRISPR/Cas9-Mediated Disease Modeling

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Abstract

Promising advances in cellular and animal models for severe diseases have been demonstrated by recent improvements in the field of gene editing techniques. The CRISPR/Cas9 technique is covered in length in this overview, with an emphasis on its most recent uses in the development of cellular and human disease models. The importance of these models in comprehending the underlying mechanisms of sickness and creating possible treatments is highlighted. The prospects and potential uses of CRISPR/Cas9 technology in the field of biomedicine are also discussed. The value of disease modeling in expanding the understanding of illness pathophysiology and in creating new treatment approaches is highlighted. The aim of this study is to provide a thorough analysis of the present and future applications of CRISPR/Cas9 in disease modeling and treatment development.

Keywords: CRISPR/Cas9, cellular models, animal models.

CRISPR/Cas9 Aracılı Hastalık Modellemesindeki Son Gelişmeler

Öz

Ölümcül hastalıklar için hücresel ve hayvan modellerindeki umut verici gelişmeler, gen düzenleme tekniklerindeki son iyileştirmeler tarafından gösterilmiştir. Bu derlemede, CRISPR/Cas9 tekniği kapsamlı bir şekilde ele alınmış ve özellikle hücresel ve insan hastalık modellerinin geliştirilmesindeki en son kullanımları vurgulanmıştır. Bu modellerin hastalıkların altındaki mekanizmaları anlamak ve olası tedaviler geliştirmek üzerindeki önemi tartışılmaktadır. Ayrıca, CRISPR/Cas9 teknolojisinin biyomedikal alandaki potansiyel kullanımları ve gelecekteki potansiyelleri de incelenmektedir. Hastalık modellemenin hastalık patofizyolojisi anlamaya ve yeni tedavi yaklaşımları geliştirmeye katkısının değerine dair bir tartışma da yer almaktadır. Bu çalışmanın amacı, CRISPR/Cas9'un hastalık modelleme ve tedavi geliştirme alanındaki mevcut ve gelecekteki uygulamalarını kapsamlı bir şekilde sunmaktır.

Anahtar Sözcükler: CRISPR/Cas9, hücresel modeller, hayvan modelleri.

Introduction

Clustered regularly interspaced palindromic repeat (CRISPR)/CRISPR-associated protein 9 (Cas9) is a bacterial immune system DNA-cutting component that has been repurposed as a key gene editing tool, significantly altering the field of scientific research.

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It works as a precise set of molecular scissors with the ability to alter, modify, and cut a specific DNA sequence. The Cas nuclease, which binds and cuts the targeted DNA sequence, and the guide RNA (gRNA) sequence, which directs the Cas nuclease to its target, constitute the two basic components of the CRISPR/Cas9 system. Cas nuclease, which disrupts the DNA sequence of entering viruses and bacteriophages and renders them inoperable, is a component of the immune systems of bacteria. Its capacity to modulate and cleave DNA is discovered to have a biological basis, and as a result, it is quickly employed as a genome editing technique[1].

Compared to older gene editing technologies such as meganucleases, zinc-finger nucleases (ZFNs), and transcription activator-like effector nucleases (TALENs), it demonstrates genome maintenance and modifies gene functions in cells and organisms in a quick, easy, and accurate manner[2]. Furthermore, genetic codes can be altered in practically any organism, including human embryos, thanks to CRISPR/Cas9[3]. Owing to its biological adaptability, it has been investigated in several laboratory experiments related to blindness, mitochondrial disorders, genetic blood diseases, lung diseases, and important viral infections such as AIDS, COVID-19, and Huntington's disease[4].

The Mechanism of Action of the CRISPR/Cas9 System

The CRISPR system is the foundation of bacteria's and archaea's adaptive immunity. A class of enzymes known as cas nucleases is able to attach to DNA sequences and break DNA strands twice. When bacteria or archaea become infected with a virus, a Cas nuclease cuts a protospacer, which is a segment of viral DNA[5-9]. When the bacterial cells come into contact with virus fragments, this biological reaction can be preserved in the bacterial genome as an immunological memory. The term CRISPR comes from the arrangement of these fragments, which are inserted between the repeating palindromic sequences. After reinfection, bacteria may recognize and get rid of the same virus via Cas9[10].

Essential components for Cas9 activation are trans-activating CRISPR RNA (tracrRNA) and CRISPR RNA (crRNA)[11]. The complementary crRNA fits the viral spacer that is retained during the original in addition to tracrRNA functioning as a scaffold. When combined, they form a complex called a gRNA. The Cas9 enzyme verifies a short area known as the protospacer adjacent motif (PAM), which is situated downstream of the target site, prior to the cutting stage. Cas9 searches the region upstream and produces a double-stranded break (DSB) when it finds a target in the PAM[12]. DSBs cause a virus to become dysfunctional because viruses lack built-in DNA repair systems[13].

Establishing *In Vitro* and *In Vivo* Models for Diseases

With the development of gene-editing techniques such as ZFNs, TALENs, and CRISPR/Cas9, the generation of human disease models has gained increasing importance due to their flexibility, efficiency, and ease of use. These models are essential tools for understanding disease mechanisms and developing novel therapies. Through the replication of critical elements of disease pathophysiology in carefully regulated experimental environments, researchers can analyze the molecular, cellular, and

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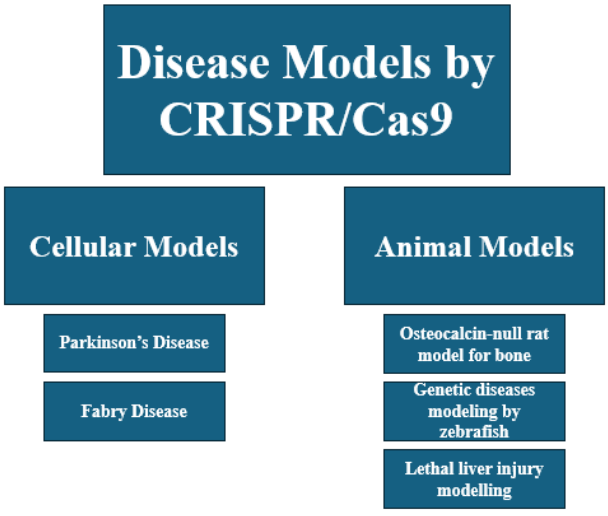
physiological mechanisms implicated in the initiation, advancement, and consequences of diseases, specifically understanding the disease mechanism[2]. Through examining how genetic or pharmaceutical treatments affect disease phenotypes, scientists are able to identify particular cellular processes or molecular pathways that can be targeted by medications or other therapeutic approaches[14]. In addition, cellular and animal models have a critical role in the development of preclinical drug and drug discovery, and by these models, significant information about the safety and efficacy of those drugs before they are tested on humans. Personalized medicine techniques are made possible by those disease models and represent the unique genetic and molecular characteristics of patients. Furthermore, identifying biomarkers is another critical application of creating cellular and animal disease models.

Disease Models Generated Using CRISPR/Cas9 Technology

By the invention of designed ZFNs, TALENs, and most recently, CRISPR/Cas9, disease models have gained attention in the field of genetics[15]. In this review, recent advances in cellular and animal models of human diseases, their importance, perspectives, and future applications are discussed (Figure 1)[16].

Figure 1. Disease models by CRISPR/Cas9



In Vitro Disease Models Using CRISPR/Cas9 Technology

Parkinson's Disease

Parkinson's disease (PD) is a neurodegenerative condition characterized by the gradual loss of dopamine-producing neurons in the brain, with dopamine being a key neurotransmitter involved in regulating movement, emotion, and cognition[17]. The pathophysiology of PD involves multiple pathways, including neuroinflammation, mishandling of proteins, mitochondrial failure, oxidative stress, and α-synucleinopathy[17].

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Vermilyea et al. used CRISPR/Cas9 gene editing to introduce the Parkinson's disease–associated LRRK2 G2019S mutation into common marmoset embryonic and induced pluripotent stem cells. The edited cells exhibited increased kinase activity, elevated ROS production, decreased neuronal viability, and reduced neurite complexity, mirroring phenotypes seen in human PD patient-derived neurons. Notably, these alterations were absent in cells with a truncated LRRK2 kinase domain. The study highlights the common marmoset as a promising nonhuman primate model for investigating PD pathogenesis and therapeutic strategies[17].

Fabry Disease

The X-linked lysosomal storage condition known as Fabry disease (FD) is typified by reduced activity of the GLA gene-encoded α-galactosidase A (α-GalA) enzyme. Treatment of FD depends on the restoration of α-GalA activity; however, it has some limitations in clinical efficacy, including the production of antibodies by the decline in plasma Gb-3 levels[18].

This study aimed to determine whether a kidney organoid system produced from human induced pluripotent stem cells (hiPSCs) might be used to recover the phenotype of Fabry disease nephropathy (FDN) by CRISPR/Cas9-mediated reduction of A4GALT. Kidney organoids model is created by the hiPSCs to establish the globotriaosylceramide (Gb-3) deposition, and also the function of alpha-galactosidase-A enzyme (α-GalA)[19].

Animal Models

Osteocalcin-null rat model for bone

Osteocalcin, also called bone γ-carboxyglutamate protein (Bglap), makes up around 1% of the total protein in the body and is the noncollagenous protein that is most prevalent in bone. According to a mouse model with osteocalcin deficiency, osteocalcin functions as a negative regulator of bone growth[20]. The mouse model also suggested that osteocalcin is an intermediary in the skeletal control of metabolism, male fertility, and cognition; however, the importance or role of osteocalcin in humans remains uncertain[21].

In osteocalcin-deficient mouse models, osteocalcin has been identified as a negative regulator of bone growth. To further investigate this relationship, a CRISPR/Cas9-generated osteocalcin-null rat model was developed to examine the complete absence of osteocalcin and its systemic effects. The purpose of the osteocalcin-null rat model is to understand the full loss of osteocalcin in the body and the results of it. According to Lambert et al., the rat could serve as a convenient system for animal modelling to study the function of osteocalcin in humans due to the consistency and similarity between the human and rat osteocalcin gene locus by using the CRISPR/Cas9 gene editing technique. The full absence of osteocalcin in the rat impacted structure and the function of bone, with increased trabecular bone and enhanced bone strength, as seen in the osteocalcin-deficient mouse model. According to this model, osteocalcin protein is completely lost in response to multiple alleles and body composition has not been affected by loss of osteocalcin[21]. Overall, the osteocalcin-null rat model provides an important platform to

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clarify osteocalcin's role in bone physiology and to evaluate its potential implications for human skeletal health.

Genetic diseases modeling by zebrafish

The zebrafish became a standard developing model and embryological model in biomedical research as early as the 1930s. Since then, a number of significant discoveries have been made to address the mysteries surrounding vertebrate development by utilizing its embryological malleability[22].

It has been demonstrated that the zebrafish is an effective vertebrate model for chemical screening and disease modeling according to its advantages including a high level of genetic homology with humans, convenient molecular size, optical transparency[23].

In a screening model by zebrafish, some small molecules are selected including dorsomorphin, crucial substance for preclinical study against anemia and fibrodysplasia ossificans progressive (FOP), fenfluramine, a serotonin inhibitor and currently developing for the treatment of Dravet Syndrome, prostaglandin, which is advanced to a therapy for cord blood transplantation, visnagin, which is significant for the protection of doxorubicin-induced cardiomyopathy[24]. CRISPR/Cas9 technology has played a central role in generating zebrafish models for human genetic diseases. By enabling targeted gene knockouts and knock-ins, CRISPR/Cas9 allows researchers to replicate specific human disease mutations in zebrafish, facilitating functional studies and drug screening[25].

Lethal liver injury modelling

The autosomal recessive hereditary condition known as hereditary tyrosinemia type I (HT1) occurs due to a deficiency of fumarylacetoacetate hydrolase (FAH), which is the last enzyme in the tyrosine breakdown pathway. In the course of HT1 pathogenesis, tyrosine and electrophilic of tyrosine metabolites the accumulation of fumarylacetoacetate (FAA) and succinylacetone (SA) rises to dangerous levels, which cause severe damage and occasionally even death to cells in the kidneys, liver, and other vital organs[26].

The $FAH^{-/-}$ pig is selected for the modelling of this disease, by using CRISPR-Cas9 in conjunction, a novel FAH biallelic mutant pig model that resembles human HT1 is created. Research revealed that it is possible to produce FAH−/− pigs in a single step without requiring outbreeding between FAH heterozygotes, significantly cutting expenses and the breeding cycle. In addition, FAH−/− pigs showed that the expression of genes coding for inflammatory cytokines are decreased respectively[27].

Advantages of CRISPR/Cas9 in cellular and animal disease models

Researchers can alter certain genes with astonishing accuracy thanks to CRISPR/Cas9, which enables highly targeted genome editing. Because of its accuracy, there are fewer off-target effects and fewer accidental mutations. The specificity of RNA is determined by its design; rather than requiring the creation of a protein, RNA alone can target any

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given region within the genome. Thus, in contrast to ZFNs and TALENs, this offers a straightforward and affordable technique. Editing genes in a variety of creatures, including cells and animals, is possible with CRISPR/Cas9. Because of its adaptability to a wide range of cell types and species, it is a useful tool for a wide range of research applications[28].

In cellular and animal disease models, with CRISPR/Cas9, particular genes linked to the pathophysiology of diseases can be precisely edited. With great accuracy, researchers can investigate the role of target genes in the onset and progression of disease by introducing mutations linked to the disease, repairing genetic abnormalities, or knocking them out. Compared to conventional approaches, CRISPR/Cas9 enables the quick creation of cellular and animal disease models. Because of the great adaptability of CRISPR/Cas9 technology, scientists may develop a broad variety of disease models in a variety of cell types and animal species. This adaptability makes it possible to replicate a wide range of human diseases, including infectious diseases, cancer, neurodegenerative diseases. Utilizing CRISPR/Cas9 technology, disease models are useful platforms for testing and assessing the safety and efficacy of new treatments. Preclinical drug discovery research can make use of these models to find promising candidates for additional development[29].

Limitations and Challenges of CRISPR/Cas9 in Disease Modeling

Although CRISPR/Cas9 technology offers unprecedented precision and versatility in genome editing, several limitations should be considered when applying it to cellular and animal disease models. One of the major concerns is the potential for off-target effects, where unintended genomic sites are cleaved, possibly leading to undesired mutations and altered phenotypes. Additionally, the efficiency of CRISPR/Cas9-mediated editing can vary depending on the target sequence, delivery method, and cell type, which may affect reproducibility across different experimental systems. Another limitation is the incomplete mimicry of complex human disease phenotypes in model organisms, as differences in physiology, immune responses, and lifespan may influence translational relevance. Furthermore, ethical issues arise when applying this technology in germline editing or in higher-order animals, and regulatory frameworks for its clinical use are still evolving. Delivery of CRISPR/Cas9 components to specific tissues in vivo remains a technical challenge, particularly for diseases affecting multiple organs. These drawbacks have been comprehensively reviewed in recent literature, highlighting the importance of optimizing guide RNA design, improving delivery systems, and conducting rigorous off-target analysis to ensure safety and reliability in both research and therapeutic contexts[30].

Perspectives and Future Applications

The development of disease models presents major potentials for the improvement of our knowledge in the field of disease mechanisms, finding new therapeutic targets, and creating more effective treatments. By using the patient derived cellular and animal models researchers can investigate the possible causes, consequences of diseases and test therapeutic approaches. Through the usage of disease models, researchers can screen vast libraries of chemicals to find possible candidates for further preclinical and clinical

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testing. In addition, in fundamental biomedical research, disease models enable the investigation of pathways, mechanisms in diseases.

In the future, precision medicine will gain more importance from the use of disease models, which offer individualized platforms for researching disease causes and evaluating therapeutic approaches. The development of targeted medicines, which are targeted to modify specific molecular targets implicated in disease pathophysiology, will continue to be driven by disease models. By allowing the screening of current medications for novel indications or therapeutic uses, disease models will play a role in the repurposing of pharmaceuticals.

Conclusion

The improvement of editing techniques has resulted in the creation of extremely adaptive approaches for studying human illnesses and furthering scientific research. Disease modeling is a potential method in this area. Researchers have used several model systems to get a better understanding of the mechanisms behind disease pathology and to find new treatment targets. These model systems include in vitro organoid systems, which replicate tissue architecture and function in a controlled environment; animal models, which provide a more complex and physiologically relevant context; and cellular models, which enable precise manipulation and observation of specific cellular processes. Disease modeling has enormous promise in the field of medication development and discovery. Scientists can improve their understanding of illness development and evaluate the efficacy of novel therapies by replicating disease circumstances in these various models. This method not only aids in the discovery of prospective drug candidates but also in adapting therapy tactics to specific disease pathways. Furthermore, illness modeling helps to develop medicinal applications, ensuring that they are ready for clinical usage. Ultimately, this improves patient care by allowing for the creation of more effective and tailored therapies. Biomedical research is making great progress toward improving disease treatment and patient outcomes as modeling approaches evolve.

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