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CRISPR: Challenges and Quantum Perspectives

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Abstract

This review examines CRISPR-Cas technology, highlighting its potential and limitations in gene editing. While CRISPR enables precise DNA modifications for treating genetic diseases, its in vivo application faces major hurdles: low editing efficiency, delivery challenges, and off-target effects. In addition, homology-directed repair (HDR) is inefficient, delivery methods are complex, and unintended mutations pose risks.

A quantum-like genetic computation hypothesis suggests that CRISPR functions within a non-linear, probabilistic framework, challenging conventional methodologies. Moreover, ethical concerns include safety, consent, and legal regulation. This review therefore argues for a new quantum-informed research approach, integrating holistic, non-invasive methods like holistic medicine and nutrition to balance genetic interventions with natural biological processes.

Keywords: *Computational Biology; CRISPR-Cas; Gene Editing; Genome Modification; DNA Repair; Cas9 Enzyme; Genetic Engineering; Homology-Directed Repair (HDR); Non-Homologous End Joining (NHEJ); Off-Target Effects; Delivery Challenges; Viral Vectors; Nanoparticles; Liposomes; Electroporation; Microinjection; Immunogenicity; Mutation Risk; Quantum-Like Computation; Lateral Gene Transfer (LGT); Horizontal Gene Transfer; Genetic Plasticity; Phenotype vs Genotype; Therapeutic Applications; Ethical Concerns; Biological Toxicity; Gene Therapy; Precision Medicine; Quantum Biology; Non-Invasive Treatments; Holistic Medicine; Self-Healing Ability; Cellular Balance; Information Encoding; Biochemical Reactions; Protein Interactions; Bacterial Immunity; Spacer Acquisition; Genetic Pathways; Molecular Diagnostics; Public Decision Making*

Importance

CRISPR is a ground-breaking tool for editing DNA and has the potential to cure diseases and improve crops, but real-world applications face major hurdles. Challenges like unintended mutations, delivery issues, and unpredictable effects must be solved for safe human use. This review highlights these obstacles and introduces a quantum-inspired perspective, suggesting genetic processes are more interconnected than previously thought. By rethinking gene editing within a holistic, balanced framework, this research advocates for safer, natural approaches to maximise benefits while minimising risks.

Introduction

Genetic engineering is a cutting-edge field offering endless possibilities for improving the quality of life. These cutting-edge methods involve modifying the genetic composition of cells to create new or enhanced organisms. This is achieved by transferring genes within or between species using recombinant DNA techniques and artificial DNA synthesis. The result is the creation of a DNA construct that can be inserted into the host organism. Gene engineering aims to fix inherent defects, such as genetic diseases, and can bring relief to millions of people worldwide. The field of gene editing is becoming more versatile, offering new possibilities for research and development amidst declining costs and further technological achievements, and the world is therefore a better place because of these advancements [18].

CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats) is a technology revolutionising the genetic research landscape and applications as an innovative gene-editing technology. It is typically used with the Cas (for CRISPR-Associated) proteins (such as Cas9) for precise genome editing.

CRISPR facilitates the rapid, efficient, and affordable correction of genomic mistakes and the regulation of gene expression in cells. It is widely used in laboratories across the globe for the fast generation of animal and cellular models, functional genomic screens, and real-time imaging of the cellular genome [13].

Mechanism of CRISPR

In the process of CRISPR-Cas gene editing, scientists first identify the sequence of DNA that causes a health problem. They subsequently create a specific guide RNA that recognises the particular strings of DNA components in that sequence. The guide RNA is then attached to the DNA-cutting enzyme, Cas, and introduced to the target cells. The complex locates the target DNA sequence and cuts it, and scientists can then modify, delete, or insert new sequences to edit the

genome. Essentially, CRISPR-Cas thus acts as a cut-and-paste tool for DNA editing [7].

Emmanuelle Charpentier and Jennifer Doudna of the University of California, Berkeley, were recently awarded the prestigious 2020 Nobel Prize in Chemistry for their remarkable and truly groundbreaking discovery of CRISPR/Cas9 genetic scissors [3]. Their innovative research has demonstrated the potential to cure genetic illnesses in mice by fixing specific damaged DNA. Moreover, the possibility of modifying human embryos using this technology is being explored, and it is exciting to note that gene therapy, the treatment of infectious diseases such as HIV, and engineering autologous patient material to cure cancer and other disorders are all promising therapeutic applications of CRISPR/Cas9 [16].

Advances in CRISPER-Cas Research

In 2005, Daniel H Haft and colleagues revealed 41 new CRISPR-associated (CAS) gene families, in addition to the four already known. They also stated that CRISPR systems belong to various classes with distinct repeat patterns, gene sets, and species ranges. These mobile genetic elements are beneficial and may be essential in driving prokaryotic evolution. However, in a dynamic balance environment, most of these elements rapidly come and go from their host genomes [6].

A Hypothesis: A Quantum Computational Lens on Gene Evolution

CRISPR systems are highly diverse and adaptable, with repeats exhibiting significant structural and functional variability. The literature identifies that major CRISPR subtypes are intricately associated with different patterns of Cas proteins, and dynamic evolutionary behaviour is represented by CRISPR loci. The subtypes are commonly passed from one species to another via lateral gene transfer (LGT) rather than through evolutionary lineages. Through horizontal gene transfer, CRISPR/Cas loci can spread between species and are not permanent. Reverse transcriptase domains are present in some but not all Cas1 proteins, suggesting that the processes behind the many CRISPR/Cas subtypes vary. Moreover, there are degraded CRISPR loci with incomplete or no Cas genes, indicating that their stability, gain, and loss are dynamically balanced during gene evolution [15].

Given the complexity of these interactions—where CRISPR elements exhibit non-linear evolutionary changes, probabilistic spacer acquisition, and modular recombination—it is reasonable to consider that the gene system functions within a quantum-like framework of biological genetic computation.

Current Situation of CRISPER-Cas in the Applications

More than 4000 different monogenic mutations cause at least 80% of all rare monogenic disorders. However, since we are aware of at least 6000 monogenic phenotypes, it is evident that this is not a comprehensive list of all the uncommon monogenic disorders [4].

The theory of CRISPR-Cas gene-editing system is remarkable for its simplicity, but it very likely leads to off-target effects and biological toxicity, with target specificity remaining a critical issue requiring improvement. In vivo editing efficiency is also lower than in vitro, making it unreliable for editing primary cells, specific tissues, and patients' bodies. Despite the challenges, many clinical trials have used CRISPR-Cas to edit patients' cells in vitro. However, when performing these procedures in a real human body environment, limited therapeutic efficacy and a lack of stability are encountered, awaiting further testing and improvement [9].

Compared to non-homologous end joining (NHEJ), homology-directed repair (HDR) is a crucial aspect of CRISPR editing because it enables precise genetic modifications using a homologous template. However, HDR is significantly less efficient in most cells, as it occurs in a specific cell cycle, while NHEJ is active throughout. Though accurate, HDR is less efficient in vivo, which limits CRISPR's reliability, thus posing a major challenge for therapeutic applications, a limitation proving critical for advancing CRISPR-based precision medicine [16].

CRISPR editing faces critical challenges during the transition from in vitro to in vivo, a crucial shift from theoretical research to practical application in the human body. The challenges raise fundamental questions about the applicability of modern research methodology. In this context, the three major obstacles in technology editing efficiency, delivery, and off-targets come into sharp focus [9].

As to the delivery, CRISPR editing may work efficiently in viral vector packaging, but not safely enough to correct gene defects and reach a new healthy balance. Physical delivery methods, such as electroporation and microinjection [1], are often inefficient in in vivo applications because CRISPR editing therapy must efficiently negotiate large numbers of cells, targeting specific tissues in a complicated cell environment, but currently fails to avoid damage to the cellular balance due to invasiveness. Non-viral vectors (nanoparticles, liposomes, exosomes) thus require complex designs to reach acceptable delivery [10].

The complexity of the structure and repeat sequence of CRISPR/CAS means unexpected DNA modifications are highly likely to introduce off-target effects. The human body may mount immune responses against bacterial Cas proteins. These challenges indicate that more than a single editing step may be needed in the complex biological environment of living bodies. CRISPR-Cas tools are applied used to correct genetic variants to cure certain diseases, but the knowns and the parts that can be manipulated are limited, while at the same time, the unknowns are unlimited in quantum-like genetic calculations in the human body [18].

Discussion in Ethics Setting

Another study discusses the ethical setting of CRISPR/CAS editing in similar domains to the challenges in previous research in three dimensions: risks/benefits, consent-related concerns, and legal concerns. The first risk/benefit mainly concerns safety, whereby gene modification is a critical decision that may not be easily reversible and may even lead to a dynamic imbalance in the bottom layer of biological cell systems. The other two dimensions of consent and legal con-

cerns highlight the requirements to improve research methodologies and applications [8]. These factors all prompt the fundamental discussion, which is increasingly moving towards establishing a new research methodology to solve quantum biological genetic computing challenges.

CRISPR Discussion in Quantum Setting

The simplicity of gene-editing technology is an inherent weakness in the quantum biological setting, not only within the scope of quantum technology research, but also radically in the methodology of research from the quantum perspective. CRISPR faces challenges and risks in quantum biology application, such as mutation, immunogenicity, and genotype vs. phenotype. Quantum biology involves analysing the real biological environment through quantum calculations. It is therefore essential to understand the fundamental quantum interactions that determine the properties of biological systems at the cell structure level [5].

Many biological processes convert energy into a form that can be used for chemical transformations. These processes are potentially quantum mechanical in nature and involve chemicals, light energy, reciprocal micro-magnetic and electric fields, and electron and proton transfer in chemical processes such as photosynthesis, olfaction, and cellular respiration. Scientists use computational models to simulate the interactions between microscopic components of organisms by reducing biological processes to fundamental physical and biochemical reactions. However, it is difficult to accurately study the microscopic essence of these reactions given the current technological constraints, resulting in uncertainty in the macroscopic results. To date, four main life processes affected by quantum effects have been identified: enzymatic catalysis, sensory processes, energy transfer, and information encoding [2].

Phages can evade the CRISPR-Cas immune system by randomly mutating their protospacer regions or PAM sequences. Point mutations dramatically lower the effectiveness of evading immunity in bacterial populations with substantial spacer diversity. This might be the case because the variety of spacers exerts more adaptation pressure on the virus, causing the invader to be quickly eliminated (Yang et al., 2021). Moreover, the cell might not always mend the break as intended, and we might accidentally break DNA at random locations in the genome, introducing fresh mutations that might impair the activity of other genes and cause various adverse effects depending on which genes are impacted [11].

The complexity of in vivo application might be far beyond what we can currently observe, which is reflected in the biological reaction with a single variant that appears as a "pathway". Recent studies have shown that Mu-like phages infect Pseudomonas aeruginosa and actively inhibit their host's CRISPR-Cas systems by producing anti-CRISPR (Acr) proteins. These proteins interact with components of the type I-F CRISPR-Cas interference mechanism. For example, AcrF1 and AcrF2 bind different subunits of the Cascade complex, preventing the Csy complex from binding to the target DNA. AcrF3 was found to bind the nuclease Cas3, inhibiting its function in target degradation. Similar proteins have been shown to prevent type I-E CRISPR-Cas immunity in the same organism [7]. These series of reactions may completely counteract the control effect of CRISPR-Cas, which means that there may be many other unknown factors and reactions in the known pathway which lead to immunogenicity.

Analogous to quantum states, genes are discrete rather than continuous, and the genotype-phenotype distinction matters. "Phenotype" with its actual observed properties, such as morphology, development, or behaviour is fundamental in the study of trait inheritance and evolution. [14] The new biological research method, Quantum Walks (QW), currently proposed, is more practical in the mathematical dimension than the physical perspective. As the most natural and practical phenomenon, the phenotype results from the quantum calculation of internal and external (GxE) factors highly demand a research methodology as data-driving quantum research.

Another risk of gene editing comes from the foundation of genetic research: A gene alone can neither cause an observable phenotypic trait nor be necessary and sufficient for the emergence of observable characteristics. A dynamic cellular environment, the computation of multiple additional genes, and particular physio-chemical conditions are required for gene engineering to have safe and practical effects on humans [12].

Conclusion

"From Traditional Medicine to Quantum Health: " A New Research Framework

Through this analysis, especially when addressing complex genetic problems, and with the help of the rapid development of modern quantum observation methods, we observe that the gene system is a complex quantum balance environment. There is therefore ample space to re-explore the methodology of the transformation process from traditional research to clinical application.

New means of quantum medical observation may include non-invasive, non-drug-based, and reversible natural methods such as traditional Chinese medicine, lifestyle regulations, comprehensive nutritional formulas, and psychotherapy. It will be important to use quantum quantative and data-driving statistical methods to evaluate and compare objective overall health indicators before and after entering the above treatment pathways. Coordinating the balance of the body's biological environment and making enhanced immunity and self-healing ability the primary goals can ensure that treatment methods promoting overall health are sufficiently safe and effective.

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