REVIEW ARTICLE OPEN ACCESS

Revolutionizing Endodontics: Potential, Challenges and Ethical Concerns of CRISPR Technology in Endodontics

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ABSTRACT

In the evolving landscape of endodontic therapy, our primary objective revolved around maintaining dental pulp vitality or intervening effectively when the pulp is irreparably damaged or infected. At the forefront of these groundbreaking advancements stands CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats) gene-editing technology that has captivated the global scientific community. The origins of CRISPR hail from a natural defense mechanism employed by bacteria and archaea. These microorganisms capture snippets of DNA from invading viruses, creating a genomic library that serves as a historical record of past viral encounters. This remarkable natural process has paved the way for potentially transformative methods in treating a spectrum of dental pulp diseases and disorders. However, integrating CRISPR into clinical practice is not without its complexities and moral dilemmas. One of the foremost concerns is the reliability of the gene-editing process. To address this, there is a concerted effort within the scientific fraternity to refine the Cas9 enzyme further, to enhance the design of guide RNAs, and to develop sophisticated techniques for identifying and rectifying any inadvertent genetic modifications. In summary, the horizon of endodontic therapy is becoming increasingly promising, with CRISPR technology leading the charge. Hence, the objective of this review article was to provide a comprehensive overview of the potential, challenges, and ethical concerns of using CRISPR technology in the field of endodontics.

Keywords: Endodontics, CRISPR, Cas-9 Systems, Gene Editing, Genetic Engineering.

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Doi: 10.36283/PJMD13-3/022

How to cite: Sajjad I,Sajid M, Abidi SYA,Lone MM Revolutionizing Endodontics: Potential, Challenges and Ethical Concerns of CRISPR Technology in Endodontics. Pak J Med Dent. 2024;13(3): 160-166. Doi: 10.36283/PJMD13-3/022

Received: : Sat, Nov 11, 2023 **Accepted:** Tue, June 11, 2024 **Published:** Wed, 24 July 2024

INTRODUCTION

Endodontics, the branch of dentistry concerned with the study and treatment of dental pulp and periapical tissues, has witnessed remarkable advancements over the years[1,2]. Among these, the emergence of CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats) technology stands out as a potential game-changer. CRISPR, originally discovered as a

bacterial immune system, has been harnessed for precise genome editing, holding immense promise in various fields including endodontics.[3, 4]

This literature review aimed to delve into the potential, challenges, and ethical considerations surrounding integrating CRISPR technology in endodontics. By examining current research and scholarly discourse, we aimed to provide insights into the transformative impact of CRISPR on endodontic procedures, while also addressing the ethical implications and regulatory hurdles associated with its implementation.

METHODS

Our literature review employed a systematic approach to identify relevant studies on the application of CRISPR technology in endodontics. The following research engines were utilized: PubMed, Web of Science, and Scopus. Grey literature was also searched by using Google Scholar. Keywords and phrases related to CRISPR technology and endodontics, such as "CRISPR", "Cas-9 gene", "Clustered Regularly Interspaced Short Palindromic Repeats", "endodontic therapy", "genetic engineering" "dental pulp" were used to search for relevant literature, without any restriction on the period of publication. All articles retrieved and found to be relevant to CRISPR technology and its potential in Endodontics, the challenges to the use of this technology including the ethical concerns were included for the review.

DISCUSSION

Endodontics, a vital and specialized field within dental medicine, is dedicated to the diagnosis and treatment of conditions affecting the dental pulp. This area within the tooth is not only crucial for tooth vitality but also complex, consisting of nerves, blood vessels, and stem cells. Endodontic therapy has two important purposes; preserving the healthiness of dental pulp whenever possible and replacing it when found infected or damaged. Root canal treatment is one of the well-recognized procedures in this field. This complicated process engages the cautious clean-up and shaping of the root canal system, followed by its filling with a biocompatible material1. Despite its efficacy, root canal therapy is not without difficulties. Important concerns include insufficient bacterial clearance, possible tooth structure degradation, and a higher risk of tooth fractures[2,5].

These challenges have catalyzed a growing interest in exploring alternative or supplementary therapies within endodontics, particularly focusing on innovative methods like pulp regeneration and gene therapy. These cutting-edge approaches are geared towards restoring the natural structure and functionality of the dental pulp, enhancing its healing capabilities, and aiming to prevent or reverse conditions like pulpitis, a common inflammatory condition[4, 6].

CRISPR: EXPLORING THE TECHNOLOGY

CRISPR, an acronym for Clustered Regularly Interspaced Short Palindromic Repeats, has become a cornerstone in the realm of these advanced endodontic strategies. This groundbreaking gene-editing technology has made a profound impact across various scientific disciplines[3]. When combined with Cas-9, a protein that functions as extremely accurate molecular scissors, CRISPR allows for targeted and exact DNA alterations. This technology uses CRISPR sequences to identify and neutralize viral DNA (Figure 1).

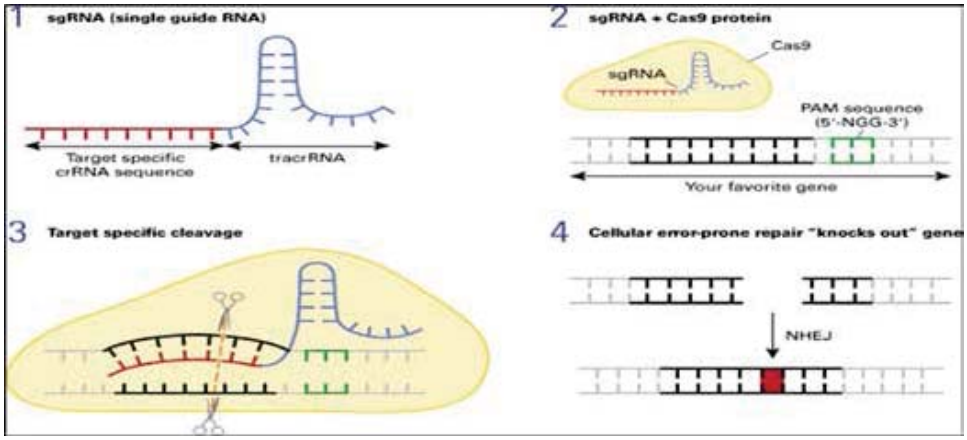

Figure 1: Principle of CRISPR/Cas9-mediated gene disruption. (1) Single guide RNA (sgRNA), comprising of crRNA sequence specific to the DNA target, and tracrRNA sequence that interacts with the Cas9 protein, (2) binds to the recombinant form of Cas9 protein with DNA endonuclease activity. (3) The resulting complex causes target-specific double-stranded DNA cleavage. (4) The cleavage site is repaired by a nonhomologous end joining (NHEJ) DNA repair pathway, that results in insertions/deletions (INDELs) to disrupt gene function [7].

 DOI: https://doi.org/10.36283/PJMD13-3/022

It was first discovered as a defense mechanism in bacteria and archaea. This natural system has been cleverly repurposed in lab settings to target and change particular regions of the genome in a variety of organisms. This has enormous ramifications because major progress is being achieved in fields including environmental preservation, biotechnological innovation, medical cures, and agricultural development[4]. A major advancement in endodontic research and practice is the incorporation of CRISPR. Researchers and medical professionals are creating new avenues for treating diseases and ailments affecting the dental pulp by utilizing this technology. More effective and less invasive endodontic treatments are now possible thanks to the accuracy and efficiency of CRISPR-Cas9 systems, which provide a level of control and specificity not possible with previous genetic alteration techniques. The potential uses of CRISPR in endodontics are expected to grow as research advances, providing promising opportunities for the field's future.

CRISPR'S ROLE IN ENDODONTICS

a. Pioneering Pulp Regeneration: In endodontics, CRISPR technology is leading the way in transforming pulp regeneration. Root canal therapy, which entails replacing the injured pulp, has been the accepted treatment for cases of irreversible pulpitis. Even though this is a tried-and-tasted technique, it frequently causes the tooth's structural integrity to deteriorate. By potentially altering particular genes to lower inflammation and encourage the dental pulp's natural healing process, CRISPR offers a ground-breaking substitute. This gene-editing skill has the potential to revolutionize the way dentists treat pulp regeneration. Moreover, new directions for more natural and successful pulp restoration are made possible by CRISPR's capacity to improve the regenerative qualities of dental pulp stem cells. (Figure 2) This may result in therapies that retain the tooth's inherent vitality as well as its strength[6–8].

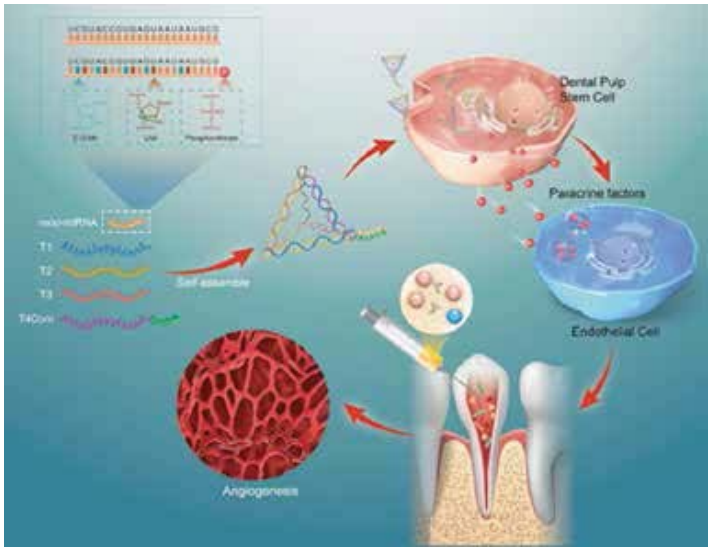

Figure 2: Modifying RNAs through CRISPR or chemical modifications to promote angiogenesis in regenerative endodontics[8].

b. Tailoring Personalized Treatments:

Personalized medicine is becoming increasingly important in various medical fields, and endodontics is no exception. The unique genetic makeup of each patient plays a crucial role in how they respond to different treatments, including those in endodontics[9-10]. CRISPR technology holds the potential to revolutionize this aspect by enabling the customization of treatments to align with individual genetic profiles. This could involve modifying genes that influence how a patient responds to anesthesia or how their tissues heal post-treatment. Such personalized approaches could significantly enhance the safety and effectiveness of endodontic treatments[11]. By tailoring treatments to the genetic specifics of each patient, dental professionals can ensure more predictable and successful outcomes, reducing the risk of complications and improving overall patient experiences[12, 13].

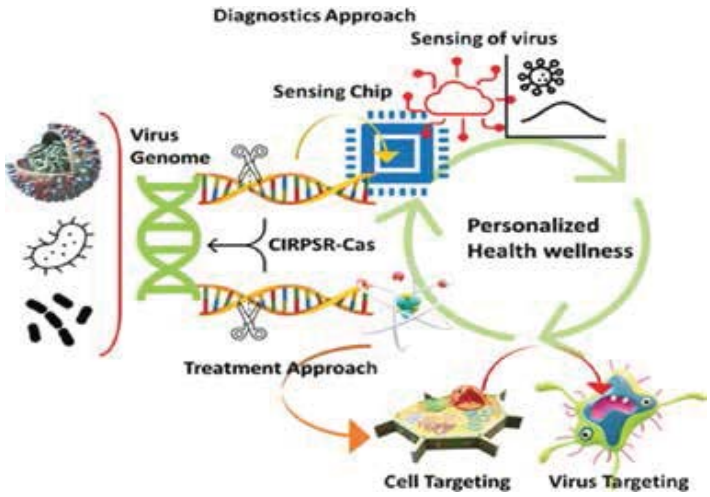

Figure 3: CRISPR/ Cas system for efficient diagnostics and treatment of diseases, tailored towards personalized health management[9].

c. Combatting Bacterial Infections:
Endodontic infections, typically caused by a diverse array of bacteria, present significant challenges to traditional antibiotic therapies. These infections can be stubborn and resistant to conventional treatment methods[14-16]. CRISPR offers a novel and highly targeted approach to tackling these infections[17]. By specifically targeting and disrupting the genes of the bacteria responsible for the infection, CRISPR can provide a more focused and effective treatment. This precision in targeting pathogens could revolutionize the way endodontic infections are treated, moving away from broad-spectrum antibiotics, which often come with the risk of promoting antibiotic resistance[17, 18]. The use of CRISPR in this context not only holds the promise of more effective treatment outcomes but also contributes to the broader fight against antibiotic resistance, a major concern in modern medicine (Figure 4) [17, 19].

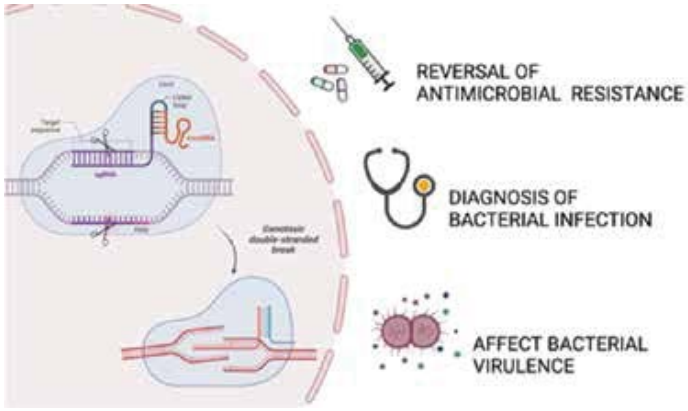

Figure 4: Key elements and applications in combating bacterial infections[17].

CONFRONTING CHALLENGES AND ETHICAL ISSUES
The application of CRISPR in endodontics, while filled with promise, is accompanied by significant challenges and ethical considerations. A primary issue is the accuracy of CRISPR's genetic edits. Although it represents a more precise tool compared to previous gene-editing methods, the risk of unintended genetic alterations remains[9]. Ongoing efforts are focused on enhancing CRISPR's specificity and accuracy, such as developing more refined Cas9 variants, improving guide RNA design, and creating methods to detect and correct accidental genetic changes[10]. These advancements are crucial for realizing the full potential of CRISPR in endodontics responsibly and effectively. The integration of CRISPR, a sophisticated gene-editing tool, into endodontic practices brings forth a spectrum of ethical considerations that require thoughtful navigation:

i. Essential Nature of Comprehensive Consent: In the

 DOI: https://doi.org/10.36283/PJMD13-3/022

realm of endodontic treatments enhanced by CRISPR technology, the principle of informed consent becomes increasingly intricate. It extends beyond mere procedural understanding to a deeper comprehension of gene editing's broader consequences. Patients must be cognizant of the possibility of accidental genetic alterations, which might have implications extending well beyond the initial treatment[20, 21]. The stakes are even higher with germline editing, where DNA modifications could be inherited by future generations who haven't consented to these changes[22]. Furthermore, the way different societies and culture's view gene editing significantly influences patient choices. Recognizing these diverse viewpoints is crucial in ensuring that patients' decisions regarding their treatment are genuinely informed and considerate of these broader aspects[23].

ii. Ensuring Fairness and Accessibility: The introduction of CRISPR in the field of endodontics brings to the forefront critical issues of fairness and justice within healthcare[24]. A major concern is the potential limitation of these advanced treatments to those who can financially afford them, thereby intensifying existing disparities in healthcare access. This is particularly problematic in regions where dental care resources are scarce, as the introduction of such sophisticated technologies could further widen the gap between different socio-economic groups. Additionally, the use of CRISPR for non-therapeutic purposes, like aesthetic dental enhancements, could create a new kind of disparity based on genetic modifications. Therefore, it is ethically imperative to ensure that CRISPR treatments are accessible to all, irrespective of their economic status[20,21,24].

iii. Safeguarding Genetic Information: The application of CRISPR in dental treatments involves dealing with delicate genetic data, necessitating stringent privacy protections[25]. The integration of genetic testing into personalized treatment plans introduces the risk of this sensitive information being exploited by external entities, such as employers or insurance firms. This raises serious concerns about privacy violations and the potential for genetic discrimination. Additionally, the inadvertent revelation of familial or ethnic information through genetic data adds another layer of complexity to the privacy issues at hand[26].

iv. Evaluating Long-term Implications: A significant challenge in the application of CRISPR for endodontic treatments is the uncertainty surrounding their long-term impacts[27]. Despite the promising benefits, the risk of unexpected outcomes remains. This necessitates a thorough ethical evaluation regarding the use of this technology in clinical settings. Establishing systems for ongoing monitoring of the safety and effectiveness of these treatments over time, and developing protocols to address any unforeseen adverse effects, are critical. An ethical balance must be struck between the potential risks and benefits, not just for individual patients but for society at large[24, 27].

v. Regulatory Hurdles: The swift progression of CRISPR technology has outstripped the development of appropriate regulatory frameworks to oversee its application[28]. This presents a significant challenge in ensuring the ethical and responsible use of CRISPR in dental practices. The varied uses of CRISPR, its worldwide reach, and the unknowns about its long-term effects complicate the creation of all-encompassing guidelines. Additionally, the differing legal, ethical, and cultural standards across nations add to the complexity of formulating a cohesive regulatory strategy. International cooperation is vital in establishing uniform standards that guide the ethical application of CRISPR in endodontics[21, 28].

vi. Importance of Public Engagement: Active public engagement in discussions about CRISPR's role in endodontic practices is crucial for aligning the technology's application with societal norms and needs[29]. This involves bringing together patients, dental professionals, and the broader community to deliberate on CRISPR's implications. Developing a comprehensive grasp of the technology, resolving public concerns, and fostering trust in its administration all depend on this kind of involvement. Additionally, it guarantees that the application of CRISPR is inclusive and considerate of the many viewpoints and needs of all parties involved[30]. The development of laws and procedures that are sensitive to the moral, societal, and cultural implications of CRISPR application in endodontics is greatly aided by this discourse[20, 31].

FORWARD-LOOKING PERSPECTIVES

The area of endodontics is entering a transformational era with the introduction of CRISPR technology, which promises less invasive and more successful treatments. However further investigation and ongoing innovation are needed to fully realize this potential. Finding certain genes that can be targeted for pulp regeneration is a crucial area of investigation. Identifying the precise genetic sequences that can be altered to encourage spontaneous pulp repair and regeneration, requires studying the complexities of dental genetics[20]. Additionally, research is still being done to determine the best safest, and most effective ways to administer the CRISPR-Cas9 system straight to the dental pulp. To ensure that the delivery method is accurate and causes the least amount of disruption, it is necessary to carefully balance efficacy and safety [32, 33].

Deepening our knowledge of the bacterial species and genetic components that cause endodontic infections is another essential component of the study. Treatments for endodontic disorders may be revolutionized by using CRISPR-based therapies that are extremely focused and effective against these infec-

tions, thanks to the identification of these particular pathogens and their genetic composition[31, 34]. Moreover, a thorough study of the genetic variables influencing individual reactions to different procedures is crucial for the creation of personalized endodontic treatments[35]. Predictive modeling methods and in-depth genetic study are required for this[36]. Researchers can anticipate how different patients may react to different therapies by analyzing genetic data, which enables a more individualized and successful approach to endodontic therapy[13, 37].

Fostering an environment of transparent and inclusive communication between patients, dentists, and the general public is also crucial. To guarantee that a wide range of viewpoints and values are incorporated into the development and deployment of CRISPR technology in endodontics, such interaction is essential [38]. This strategy will aid in making sure that the advantages of CRISPR are achieved in a way that respects the various demands and concerns of all stakeholders and is morally and fairly applied[29, 30]. It is crucial that the dentistry community moves cautiously and with a strong sense of responsibility as it enters this new and fascinating zone. The intention is to use CRISPR's transformational potential to the fullest, minimizing dangers and raising ethical questions while optimizing benefits for patients and society [39, 40]. The secret to effectively navigating the exciting but challenging field of CRISPR in endodontics will be to adopt a balanced approach.

CONCLUSION

In recent times, there has been a major shift in dental medicine with the introduction of CRISPR technology into endodontic practices. It has the enormous potential to drastically alter the dental pulp disease treatment landscape, providing opportunities for better patient results and experiences. But this path needs to be taken with a strong commitment to moral values, and ethical considerations addressing important concerns like the accuracy of genetic editing, fair access to cutting-edge therapies, protection of genetic privacy, and a full comprehension of the long-term consequences of CRISPR-based interventions.

ACKNOWLEDGMENTS

None.

AUTHORS CONTRIBUTION

IS- Conceived and designed the idea, literature review and data collection, data interpretation, and initial draft of the manuscript. MS- Conceived and designed the idea, and initial draft of the manuscript. MML- Literature review and data collection, Final draft, and critical review. YAA- Data interpretation, final draft, and critical review.

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