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Review Article

Precision dentistry: CRISPR in oral health

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ABSTRACT

With the technological revolution, precision medicine has become a possible entity in the present times. Genome editing, a genetic engineering tool, has added a new dimension to diagnostics and therapeutics in healthcare. Amongst the genome editing tools, CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats) stands out for its efficiency, versatility, and precision. CRISPR refers to a genetic scissor that can precisely edit specific parts of DNA accurately and comprises three steps: identification, editing, and repair. CRISPR has seen various applications in medicine from treating genetic and infectious diseases to cancer therapy. In dentistry, CRISPR technology is in its initial stages and has shown potential in periodontitis, dental caries, head and neck cancer, orthodontics, craniofacial defects, and viral infections. CRISPR by host response modulation offers personalized periodontal care, inhibits biofilm formation to prevent dental caries, personalized cancer treatment by targeting responsible genes, provides genetic information on the aetiology of craniofacial malformations, and helps in understanding viral infections and targeted therapies. This customized precision approach opens new avenues to improved treatment outcomes. CRISPR technology is not devoid of challenges, it has ethical challenges, immunogenicity, and off-target effects, yet, it holds promise as a future diagnostic and therapeutic approach if implemented with care.

1. Introduction

In human history, there has been a continuous battle against diseases, and science has found several ways to combat them. Sanitation, vaccines, drugs, and surgery have been the four pillars in mitigating the illness. However, these have reached their limits over time due to evolving pathogens, resistance, and other complexities. The modern era of genetic engineering has provided a fifth dimension in diagnostic and therapeutic approaches to healthcare i.e. genome editing. This modern gene technology intervenes at a molecular level and opens up a customized therapeutic approach.[1] Genome editing is genetic engineering where DNA is intentionally removed, inserted, and modified in the living cells.[2] CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats) is one of these genome editing tools that has been adequately researched and found potential in terms of efficiency, versatility, and precision.

Before CRISPR several other genome-editing tools were adopted such as transcription activator-like effector-based nucleases (TALENs) and mega/zinc finger nucleases, however, they could not succeed due to their challenges. CRISPR was inspired by prokaryotic organisms that use this genome-editing machinery to disable invading bacteriophages or plasmids. CRISPR-Cas9 technology behaves like a very precise genetic scissor that can edit specific parts of DNA with precision. CRISPR involves 3 steps identification, editing, and repair. In comparison to older gene-editing methods, CRISPR performs with low off-target effects making it a potent tool for scientists

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and clinicians. This powerful tool can now target and disable specific genes with great accuracy opening doors to new possibilities for treating genetic conditions. CRISPR technology works by creating a short guide RNA that matches that of a specific sequence of the target DNA. This guide RNA attaches to a protein, Cas9. This binding facilitates pairing between the target DNA sequence and guide RNA. Then the Cas9 snips off the DNA at an accurate location dictated by guide RNA creating a split in both DNA strands. Following this, the cell's natural repair process initiates, this process leads to the insertion or deletion of DNA segments or the replacement of the existing DNA with customized-design sequences. The possibility to make customized changes in the DNA enables scientists to correct genetic defects or introduce desired traits.[3]

2. Discussion

CRISPR has been explored in medical, agriculture, and biotechnology domains. CRISPR technology also extends to the engineering of microorganisms for biofuel production.[4] It is expected that this technology will benefit in treating diseases, growing nutritious crops, and combating infectious diseases. In medicine, CRISPR has been explored in precision medicine, cancer therapies, infectious disease prevention, and gene therapy in curing genetic diseases like beta-thalassemia, sickle cell disease, muscular dystrophy, and cystic fibrosis. CRISPR has also found its applications in dentistry such as eliminating pathogens in periodontitis and dental caries, regenerative dentistry, management of genetic disorders, salivary gland therapies, and precision dentistry.[5–7]

2.1. Applications of CRISPR in dentistry

2.1.1. Periodontitis

Periodontitis is the most common dental disease affecting the majority of the population and conventional treatment starts from routine scaling and oral hygiene measures. When these basic measures fail, drug therapy and periodontal surgeries are proven to be of help. In some patients, these advanced surgeries fail to restore periodontal health and continual periodontitis leads to tooth loss and edentulousness. These deficiencies call for novel approaches to intervene in complex periodontal diseases and restore patients' oral functions, and CRISPR has shown promise in this. CRISPR helps in periodontal therapy by host response modulation personalising the periodontal care. Personalized care offers enhanced benefits over one-size-fits-all treatment strategies. This approach makes use of CRISPR, a genome-editing technology and has been discussed widely in literature.[3]

Several studies have investigated CRISPR–Cas9 in exploring molecules involved in inflammatory pathways of periodontal disease. With this technology, researchers could disable specific genes, PTPN2 and SOD2, and know their roles in regulating inflammation. CRISPR–CAS9 can identify cellular pathways associated with periodontal pathogenesis by targeting the molecular players involved. This helps develop possible treatment plans to enhance periodontal health.[3]

CRISPR technology by self-targeting spacer sequences, decreases the production of extracellular polysaccharides and effectively breaks down biofilm formation in Streptococcus mutans. This is significant in detecting and targeting specific sites within biofilms. The Cas3 protein, part of the CRISPR–Cas adaptive immunity system has shown potential in breaking down biofilms. Scientists have used the CRISPR–Cas3 system to deliver antimicrobials through engineered bacteriophages.[3] An in-vivo study by Selle et al targeted Clostridioides difficile using a modified bacteriophage expressing CRISPR RNAs that target the bacterial genome.[8] CRISPR–Cas9 technology in research settings helps in understanding the pathogenesis of the disease, and in clinical settings to modify host cells and biofilms' genomes to alter the course of the disease. CRISPR–Cas9 technology can create knockouts as a diagnostic tool to recognize the cellular pathways that are involved in the pathogenesis. Other CRISPR systems, CRISPRi, CRISPRa, and Cas13 can alter the transcriptome and gene expression involved in the progression of periodontitis. CRISPR system can target the biofilm to develop strategies to decrease or remove periodontal pathogens. CRISPR systems also provide therapeutic approaches to alter the nature of biofilm from disease-causing to health-promoting.[3]

2.2. Dental caries

Plaque is responsible for the most common dental problem, dental caries and streptococcus mutans are the causative agents for this. Virulent factors such as glucosyltransferases synthesise extracellular polysaccharides from sugar leading to the formation of biofilm. Gong T et al used CRISPR technology to target glucosyltransferases to inhibit the formation of biofilm. CRISPR was able to successfully edit glucosyltransferases resulting in a reduction in the formation of extracellular polysaccharides and consequently biofilm formation.[9]CRISPR technology by altering, inhibiting, and breaking biofilm formation prevents the formation of plaque the causative agent for dental caries.[3]

2.3. Head and neck cancer

Cancer is a complex genetic disease that arises due to alterations in genes and epigenetics, hence cancer treatment can immensely benefit from CRISPR technology. Several attempts to edit genes in cancer cell lines have revealed the involvement of fibronectin and LDB1 in cancer cells

and therapeutic agents such as s p75NTR and MUL1-HSPA5 axis have been identified. Researchers have used CRISPR/Cas9-edited immune cells to fight cancer cells. These findings contribute to identifying the treatment strategies for head and neck cancer.[10]

Chai et al were able to detect 918 genes associated with oral squamous cell carcinoma (OSCC) using CRISPR technology, some of which are common to other types of cancer whereas some are unique to OSCC. CRISPR also revealed that cell lines did not survive in the absence of the genes responsible for the Hippo pathway that causes cancer progression. Identifying these genes opens ways to develop new treatment strategies for cancer.[11]

To treat oral cancer, immune cells are extracted from patients and CRISPR genome editing is done in a laboratory setting. Then these genetically modified immune cells are delivered into the patient's body for cancer treatment. The CRISPR components can be delivered at the focal point of the cancer with diverse delivery methods.[10]

These possibilities in CRISPR technology for cancer prevention have opened up new doorways for diverse treatment approaches and have the potential to overcome the challenges of conventional approaches, delivering more personalized and outcome-based cancer treatment.

2.4. Craniofacial defects and tissue engineering

CRISPR has been significant in studying genes involved in craniofacial defects and how they are formed. Scientists utilized CRISPR to unveil the significance of the C-terminal domain of the Msx1 gene in the development of teeth and palate. The CRISPR system was applied to target Msx1 in mice, resulting in homozygous mice with agenesis of the lower incisor and, in some cases, cleft palate. Additionally, the MSX1 homeodomain has been detected in non-syndromic cases of tooth agenesis, premolars, and third molars. These insights guide newer treatment approaches in handling craniofacial deformities. The utility of CRISPR technology extends to the exploration of temporomandibular disorders and related pain conditions through targeted genome modifications.[10,12]

2.5. Orthodontics

Biomedical advancements offer alternative approaches to deal with challenges related to the genetic and environmental factors in malocclusion, understanding the biological processes of orthodontic movement, influencing growth patterns, and achieving post-treatment stability. CRISPR can identify genes responsible for craniofacial malformations and can modify and fix these genes for favourable outcomes. Although CRISPR research is in its initial stage, future applications can bring a paradigm shift in orthodontic intervention.[12]

2.6. Viral infections

Viral diseases are complex to treat because of mutations and latent infections. CRISPR technology can be used to study these mutations and identify genes, factors, or proteins that cause proliferation and latency. This helps understand the viruses to establish specific cell lines and drug development for viral infections. CRISPR system assists not only in virology research but also prevention and control of latent viral infections. The CRISPR system has been studied for the interruption of latent infections for herpesviruses including herpes simplex virus (HSV), Epstein–Barr virus (EBV), cytomegalovirus (CMV), and herpesvirus associated with Kaposi's sarcoma. CRISPR can target viral genomes during latent infections to identify specific genes, factors, and proteins essential for proliferation and latency. This increases the understanding of herpesviruses to develop new drugs for viral infections.[13]

2.7. Challenges in CRISPR technology

CRISPR technology offers many advantages, yet it is not devoid of associated challenges. The need for an efficient and safe delivery system, immunogenicity, ethical issues, cell damage, and off-target effects are some of the challenges of this technology. Delivery of CRISPR components to the target area poses a clinical challenge. Host immune responses to these components can elicit untoward biological effects at times leading to lethal effects. Detecting and reducing these responses is a clinical challenge. The off-target effect when nucleases bind and edit unintended DNA sites leads to untoward genomic changes.

Basic and preclinical research offers several advantages yet the challenge is experimentation with human embryos remains controversial and illegal, and breaches privacy and confidentiality. Translational and clinical medicine has achieved promising results yet it is associated with serious injury, disability, or death of research participants, misapplications, eugenics, misuse, and damage to ecosystems.[14,15]

3. Conclusion

CRISPR is an innovative and modern technique of genetic engineering offering a multitude of applications from research to clinical applications. Yet the challenges associated with this need to be addressed for a safe and effective implementation. Research and ethical guidelines from regulatory bodies will be critical to minimize risks and maximize benefits. Research has yielded immense promise in treating diseases especially dreadful diseases like cancer, yet the associated risks necessitate ethical guidelines and careful implementation.

The field of medicine has seen many applications and advanced trials, it's noteworthy that for dentistry

CRISPR research is in its initial stage. The use of CRISPR technology in dentistry is still an emerging area and researchers are exploring its potential applications in addressing oral health issues. As dental research progresses, it may unveil new approaches for precise and personalized dental treatments.

4. Source of Funding

None.

5. Conflict Interest

None.

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