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Short Communication

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Next-Generation Phage Therapy in Dentistry: CRISPR-Cas Integration to Counter Antimicrobial Resistance and Genetic Modifications

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ABSTRACT

The rapid emergence of antimicrobial resistance (AMR) and bacterial tolerance has renewed interest in bacteriophages as alternative antibacterial agents. Beyond their natural lytic activity, bacteriophages can be engineered as delivery vehicles for CRISPR–Cas systems, enabling sequence-specific targeting of resistance and tolerance-associated genes. Phage-mediated CRISPR delivery allows selective elimination of resistant bacteria, removal of resistance plasmids, and disruption of tolerance and persistence mechanisms, including those that contribute to biofilm formation. This short communication highlights the potential of bacteriophages as programmable CRISPR–Cas delivery platforms and discusses their relevance in addressing both genetic resistance and phenotypic tolerance in oral health.

Keywords: *Bacteriophage; CRISPR–Cas; Antimicrobial resistance; Bacterial tolerance; Phage engineering*

Introduction

In the current era of rapidly evolving pathogens, the rise of antimicrobial resistance and bacterial tolerance to conventional antibiotics has become an escalating threat [1]. Each year, around 0.7 million deaths occur worldwide due to AMR pathogens, with projections suggesting this could surpass cancer-related fatalities by 2050 [2], and dentists too have their substantial share of contribution in creating this AMR world through disproportionate or inappropriate prescription of antibiotics [3]. Resistance is the evolution of permanent genomic changes that empower bacteria to defy an antibiotic and grow uninterrupted; whereas, tolerance does not involve DNA changes; instead, it is limited to a temporarily altered gene activity to slow or pause growth. [4] To overcome these developing critical issues, recently, several potential alternatives to conventional antibiotics have come into the spotlight, including bacteriophages, and these have been explored and found highly beneficial across many medical fields [3,5]. Nevertheless, bacteriophages are also subject to limitations related to the development of antimicrobial resistance and, hence, certain molecular engineering approaches, including "clustered regularly interspaced short palindromic repeats (CRISPR)-Cas," have been turned to address this issue [6].

What is CRISPR- Cas?

CRISPR-Cas is an adaptive immune system that provides bacteria with defence against invading viruses, functioning like a pair of "scissors" which aims at the specific DNA sequence of the invading virus. Owing to the ongoing research, scientists have harnessed this bacterial machinery for target-specific genomic editing

by incorporating it into engineered phages, which in turn invade respective bacteria, thereby enabling the development of programmable antimicrobial weapons [7]. The gene or DNA sequence responsible for antibiotic resistance in bacteria is identified, and the CRISPR-Cas system specific to this sequence is engineered into the bacteriophage to target these resistant bacteria. Once the bacteria are infected with these CRISPR-engineered phages, Cas nucleases and guide RNAs are released into bacterial cells, where sequence-specific DNA cleavage occurs. This facilitates targeting of resistance genes and the induction of DNA-hampering or cleavage of plasmid-borne antibiotic-resistant fragments [8]. CRISPR can also be used to target toxin-specific bacterial genes, particularly those responsible for biofilm formation and endotoxin release. A diagrammatic representation is shown in Figure 1.

This defensive machinery is of different types, CRISPR-Cas systems fall into two broad classes: Class 1 (types I, III, and IV), which depend on complexes formed by several Cas proteins, whereas Class 2 (types II, V, and VI) utilize just one large Cas protein explaining why Class 2 systems, particularly type II (Cas9), are simpler and more commonly used in genome editing [7]. This immune defence mechanism can be manoeuvred in two ways to achieve desired outcomes. One modality being precise targeting of genes involved in the development of antimicrobial resistance, thereby restoring bacterial susceptibility to the antibiotic. The second strategy employs disrupting essential genes indispensable for bacterial survival; ablation of these genetic determinants irreversibly compromises cellular viability, culminating in bacterial death. As needed, the most suitable type can be employed. Owing to its high targeting accuracy and strong operational simplicity, Cas9 has become a very popular and preferred tool [9].

This Technology comes with a baggage of advantages, the topmost being the high precision. Marked by a distinct set of nucleic acid identification, CRISPR-Cas systems enable precise and highly specific deletion and alteration of target-genomes, which offers a path to achieve striking results in the field of therapeutics. Another leverage is the self-replication of this machinery. Since the gene editing tool is delivered in an engineered bacteriophage, it multiplies along with the bacteriophage replication [9].

CRISPR-Cas Landscape in Oral Pathogens

Owing to advances in molecular technology in dentistry [10], it has been shown that oral bacteria harbor diverse CRISPR-Cas architectures that effectively provide immunity against phages [11]. Using CRISPR/Cas9 gene editing, the glucosyltransferase-encoding genes in S. mutans were disrupted. This targeted modification of key virulence factors led to a marked reduction in extracellular polysaccharide (EPS) synthesis and effectively inhibited biofilm development, such as foundational for precision caries prophylaxis [12]. Phages serve as effective vectors to deliver CRISPR-Cas machinery, enabling in situ genome editing within biofilms. This dodges delivery barriers in subgingival/endodontic niches, targeting resistance cassettes or virulence operons to resensitize pathogens or attenuate pathogenicity. Preclinical models have already demonstrated selective depletion of MDR strains while sparing

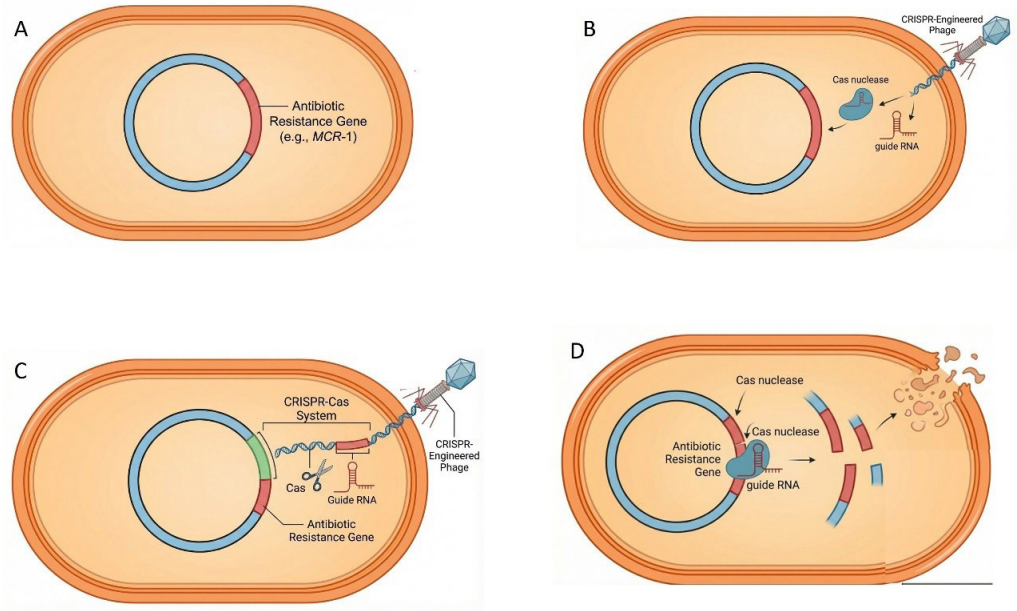

Figure 1: *Diagrammatic depictions of how the CRISPR-engineered bacteriophage works. (A) The image shows a bacterial cell containing a plasmid with an antibiotic resistance gene. (B) A CRISPR- engineered bacteriophage against the bacteria. The genetic component of this bacteriophage has been modified to include the code for the Cas nuclease and a guide RNA (highlighted in red) that is complementary to the antibiotic-resistant gene on the plasmid. The CRISPR-engineered phage injects its DNA into the bacterium. This leads to the production and release of the Cas nuclease and guide RNA (shown in red and blue) inside the bacterial cell, where they can now find their target. (C) The guide RNA has guided the Cas nuclease to the resistance gene, and the DNA is being cleaved, breaking the plasmid. (D)The Mechanism and Outcome. This process leads to the destruction of the bacterial cell.*

commensals [13], a critical advantage over antibiotics. Further, formulation innovations (e.g., hydrogel/nanoparticle carriers, mouthrinse-compatible vectors) facilitate adjunctive use post-debridement or root canal therapy, potentially reducing reliance on systemic antibiotics. In addition to microbial infection targets, CRISPR-Cas can also be used to target genes responsible for carcinogenesis and other autoimmune disorders, thereby helping prevent or better manage these disorders [14].

Conclusion

To conclude, the amalgamation of CRISPR–Cas systems and bacteriophage results in a transformative advance in the fight against antimicrobial resistance. By harnessing phages' natural lethality and CRISPR's programmability, this hybrid strategy offers targeted, adaptable, and potentially resistance-proof interventions. While hurdles in scalability, safety, and regulation remain, the trajectory from early engineering successes to ongoing preclinical triumphs suggests CRISPR-armed phages could become a cornerstone of precision antimicrobial therapy. In an era where antibiotics falter, this fusion of ancient viral warfare and cutting-edge molecular biology may prove decisive in reclaiming control over bacterial pathogens.

AI Use Statement

During the preparation of this work, the authors used ChatGPT in order to generate figures and polish the language. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

Conflict of Interest and Funding

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