Technology Offer

Temporal epigenome modulation for efficient CRISPR-Cas engineering of bacteriophages

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Lytic bacteriophages, or phages, possess a unique ability to replicate by infecting and destroying bacterial hosts, offering vast potential in medical and biotechnological fields. Their applications span across clinical and industrial sectors, including phage therapy for treating and preventing bacterial infections in humans, such as enteric diseases, skin infections, chronic conditions, and sepsis. Beyond healthcare, phages can help reduce bacterial virulence and antibiotic resistance, preserve food, disinfect surfaces, treat dysbiosis, modulate microbiomes, and even control pests in agriculture.

The engineering of phages enables the customization of their properties to suit specific applications. Modern genetic tools, such as CRISPR-Cas systems, offer precise phage engineering capabilities through site-specific mutagenesis. However, phages can evade CRISPR-Cas-mediated cleavage due to extensive DNA modifications, like cytosine glycosylation, which protect their genetic material and reduce mutagenesis efficiency. These DNA hypermodifications, while shielding phage DNA from host defense systems, present a challenge: removing enzymes involved in the DNA modification pathways can impair phage fitness. Therefore, innovative strategies are needed to achieve efficient CRISPR-Cas-based phage mutagenesis while preserving essential DNA modifications.

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Scientists from the Max-Planck-Institute for Terrestrial Microbiology addressed this challenge, enabling the engineering of phages with intact cytosine modifications, thus maintaining their biological functionality and fitness. They developed an approach to temporally modify the T4 bacteriophage epigenome. By applying the eukaryotic ten-eleven translocation (TET) enzyme, the abundance of phage DNA modifications can be temporally reduced, such that specific and efficient targeting of phage DNA with CRISPR-Cas is possible. The DNA modifications are fully reversible, as progeny of TET-treated T4 phages restore wild-type-like levels and phage fitness. By applying this approach, precise phage DNA targeting and seamless point mutation integration can be enabled. The scarless nature of the strategy allows to investigate phage epigenome functions without necessitating gene deletions. Moreover, the technique is a valuable tool for engineering of "designer phages" for synthetic biology and biotechnology This advancement paves the way for more effective and versatile phage-based solutions across medical, industrial, and agricultural domains.

Patent Information

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Publications

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