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Combatting Antibacterial Resistance With Phage Therapy

Linda Line
Southern Maine Community College, Lindaline@smccme.edu

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Southern Maine Community College, South Portland Maine

ABSTRACT

Phage therapy is the use of viruses to treat bacterial infections. This therapeutic method offers a viable solution to antibiotic resistance among pathogenic bacteria. In this review, we discuss the strengths and weaknesses of phage therapy. Phages attack specific hosts, making them more narrow-spectrum than antibiotics. Adding genes for infection-fighting peptides to the genome may improve the effectiveness of phage therapy. Antimicrobial regulator peptide IDR-1018 is involved in modulation of the immune system. A research group has shown that incorporating a gene for IDR-1018 into phage T7 significantly increased the bactericidal effects in *Escherichia coli*. In another study, phage lysin PlyF307, a peptide that lyses bacterial cells, resulted in an increased ability to eliminate biofilm when added to a genome of *Acinetobacter baumannii* strain 1791. Researchers observed promising results in a mice study with this modified phage. Studies done both *in vivo* and *in vitro* have shown that phage can be modified to enhance their ability for use in phage therapy. Further research has addressed the weaknesses of phage therapy. While specificity is a limitation, so is bacterial resistance rate. Bacteria, highly equipped organisms, have shown resistance to particular phages. Through modification of the phage genome, we can decrease the frequency of bacterial resistance while increasing bactericidal activity. These studies suggest there may be ways to modify phages to overcome the limitations of host range and host resistance.

INTRODUCTION

- Discovered in the early 1900s, phage therapy is the use of bacterial viruses, known as bacteriophages, to inhibit and destroy infectious, pathogenic, bacterial cells.
- Multi-drug-resistant bacteria have become a widespread global health concern, and the incorporation of phage therapy into the medical field offers a viable solution.
- Phages are highly specific organisms, meaning they will only infect the bacterial cells they were designed to and not the hosts' cells, eliminating the worry of harm to the human body.
- Specificity can be a limitation resulting in decreased potential of multispecies effectiveness; however, with advanced technology, scientists can overcome this issue via genome modification.
- Modification is the structural alteration of an organisms' genomic DNA/RNA through the introduction of chemicals, such as peptides or lysins.
- Lysins and immunomodulatory peptides not only increase the efficiency rate of phage but also boosts the hosts' immune system, broadens the host range, and enhances antibacterial activity.
- This review highlights the advancements in phage therapy, the importance of modification, and discusses what these successful studies mean for our future.

The Phage Life Cycle

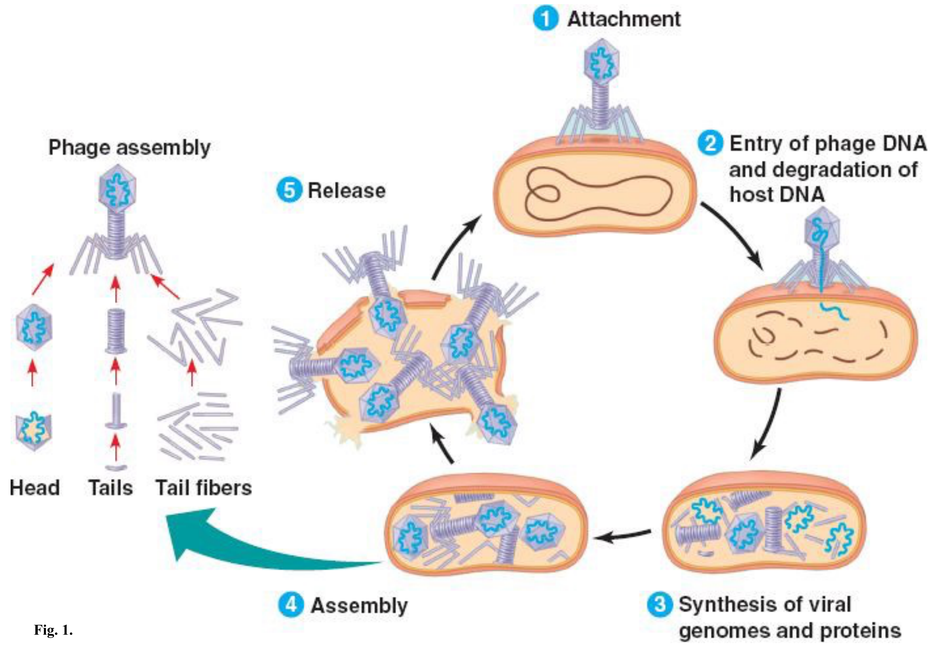

Fig. 1.

How is phage therapy useful to humans?

❑ Phage therapy has been studied for decades in countries such as Russia, France, and Egypt. One advancement is the use of phage to quickly heal topical burns and prevent infection. Scientists have used bandages, soaked in phage-enhanced liquids, in order to treat the infections of multi-drug resistant bacteria. Researchers in Egypt found clinical success when studying the antibacterial resistant *Klebsiella pneumonia.* A group of 49 infected burn victims were dressed in phage enhanced bandages for 17 days. 42 of the 49 patients resulted in complete recovery while the other 7 had partial recovery. Another study in France resulted in a 50% success rate of treating burn victims with *Pseudomonas aeruginosa* infections within 14 days.

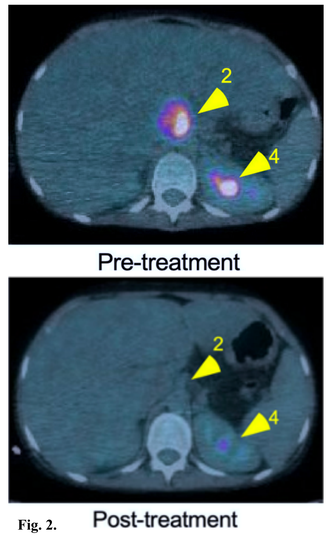

Fig. 2.

❑ Helping with autoimmune diseases. With only 1% chance of survival, a 16-year-old cystic fibrosis patient suffered from a deadly infection of antibacterial resistant *Mycobacterium abscessus* after a double lung transplant. The infection spread from the lungs to the liver and caused skin lesions. This image (**Fig. 2**) shows the infection within the patients' liver. The "Post-treatment" image is three weeks later, after receiving phage infusions twice a day, the infection is 90% inhibited. Scientists engineered a phage cocktail to treat the bacterial infection. This is the result of splicing multiple phage genomes together in order to produce one highly destructive organism. (Dedrick et al., 2019)

❑ Phage therapy has shown promising results in helping to deplete cancerous brain cells. In this specific study, researchers used modified phage M13 (of the enterobacteria family) to increase effectiveness of the alkylating agent temozolomide (TMZ). This was done by enhancing the phage genome with the TMZ agent and target receptors from glioblastoma cell walls allowing the phage to bind to the tumor. *In vivo* studies on mice have led to size reduction of tumors and also resulted in complete inhibition of cancerous cells within one month. Human trials are hoped to begin in the next few years in the UK and Europe. (Przystal et al., 2019)

How can modification of phage be beneficial?

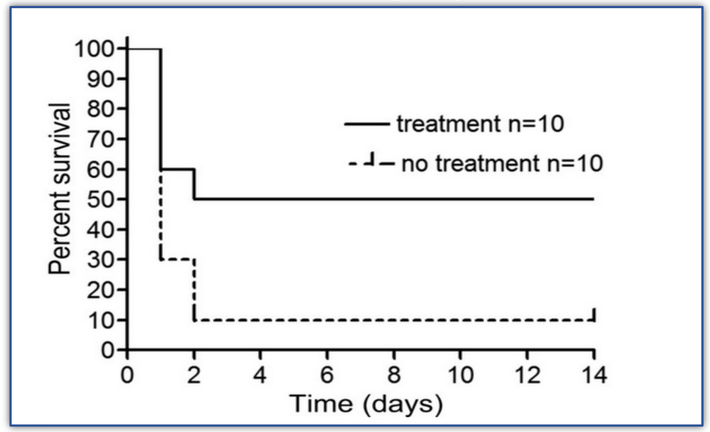

Fig. 3. Analyzing the effects of PlyF307 in *Acinetobacter baumannii* biofilms. This figure identifies the effectiveness of *in vivo* modification. Mice were infected with 10^8 CFU (Colony-Forming Units) of *A. baumannii* and two hours later injected with the enhanced strain 1791 modified lysin PlyF307 (a single domain lysozyme known to inhibit gram-negative bacteria), under the skin, for a duration of 24 hours, two doses of 1mg PlyF307 at four-hour intervals. With these results, 90% of the untreated mice died within 48hrs, while the mice treated with the lysin modified phage had a significantly higher survival rate, observing an increase of 50%. (Lood, et al., 2015)

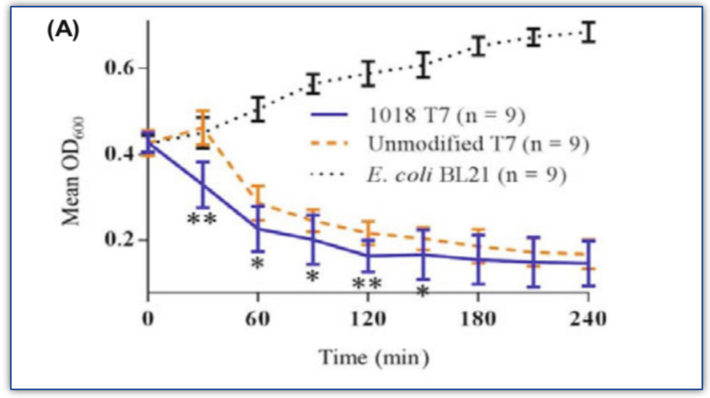

Fig. 4. Observations of unmodified T7select phage and modified 1018 T7 phage effectiveness on four-day old *Escherichia coli* BL21 biofilm. Here we analyze that the 1018 phage is more effective than T7select. Bactericidal activity was recorded within 30 minutes of initial contact whereas the unmodified T7select phage did not inhibit growth until 60 minutes. While both phages resulted in 90% bactericidal effects, the modified phage was able to destroy the infectious cells at a much quicker rate than an unmodified phage. (Lemon, et al., 2019)

CONCLUSION

This review expands upon how the genomic modification of phage may be a solution to antibiotic resistance. There has been an increase of antibacterial resistant species; with how progressive bacteria are, the need to address this issue is becoming more prevalent. Phage are abundant, highly specific, microscopic organisms that scientists can manipulate and engineer rapidly to expand the host range and generate variants to combat infectious diseases. With known success rates greater than 50% in vivo, phage research has great potential that is yet to be exploited.

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