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ROLE OF BACTERIOPHAGES IN TARGETING ANTIBIOTIC-RESISTANT BACTERIA

Rishaa Osborne Pimenta

University of Mumbai.

ABSTRACT The rise of antibiotic-resistant bacteria poses a significant challenge to global health, necessitating innovative approaches to combat these infections. Bacteriophages, viruses that specifically infect bacteria, have emerged as promising alternatives to traditional antibiotics. This review explores the use of bacteriophages as a targeted therapy to tackle antibiotic-resistant bacteria. Bacteriophages offer several advantages, including their specificity for bacterial targets, ability to evolve and adapt to bacterial resistance mechanisms, and potential for personalized treatment. The mechanisms of phage action, including direct lysis of bacteria and modulation of the host immune response, are discussed. Moreover, strategies to enhance the effectiveness of phage therapy, such as phage cocktails and phage engineering, are explored. Challenges and considerations, including safety, regulatory aspects, and bacterial resistance to phages, are also examined. Despite these challenges, bacteriophages hold tremendous potential as a valuable tool in the fight against antibiotic-resistant bacteria, offering hope for more targeted and effective treatments in the future.

KEYWORDS

bacteriophages, antibiotic resistance, bacterial infections, targeted therapy, phage therapy, personalized treatment, mechanisms of action, phage cocktails, phage engineering, safety, regulatory aspects, bacterial resistance, innovative approaches, global health.

***Corresponding Author**

INTRODUCTION :

The emergence of antibiotic resistance has posed a severe threat to public health globally. These days, even a common infection can be fatal. Due to the diminishing effectiveness of conventional antibiotics, alternative therapeutic agents are urgently needed to combat these resilient pathogens. Bacteriophages, viruses that infect and replicate within bacterial cells, have emerged as promising agents in the fight against antibiotic-resistant bacteria. Their unique ability to specifically target and kill bacteria while leaving host cells unharmed makes them attractive candidates for therapeutic interventions.

Traditional antibiotics are giving rise to multidrug-resistant strains. Limited development of new antibiotics is also a barrier. Bacteriophage therapy has gathered considerable attention as a potential solution to the challenges faced by conventional antibiotics. Bacteriophages exhibit a remarkable capacity to infect and destroy bacteria through various mechanisms, such as direct lysis of host cells or interference with essential bacterial processes.

The objective of this review article is to provide an overview of the role of bacteriophages in targeting antibiotic-resistant bacteria. We aim to explore the current understanding of bacteriophage therapy, its mechanisms of action, and its potential applications in clinical settings. Furthermore, we will examine the future prospects of utilizing bacteriophages as therapeutic agents. By exploring their therapeutic potential, and we hope to contribute to the development of innovative strategies for combating antibiotic resistance.

Antibiotic Resistance Crisis :

The antibiotic resistance crisis has emerged as a critical global health challenge, threatening the effectiveness of our most valuable tool in combating bacterial infections : Antiobiotics!

This crisis poses significant implications for patient care, public health, and healthcare systems worldwide. The extensive use of antibiotics in both human and animal healthcare has put selective pressure on bacteria, favoring the survival and multiplication of resistant strains. These bacteria have acquired genetic mutations or acquired resistance genes through horizontal gene transfer, rendering them ineffective from the antibiotics.

Hence, infections caused by antibiotic-resistant bacteria are associated with higher morbidity, mortality, prolonged hospital stays, and increased healthcare costs. One of the major concerns of antibiotic resistance is the emergence of multidrug-resistant organisms (MDROs), which are resistant to multiple classes of antibiotics. MDROs such as methicillin-resistant Staphylococcus aureus (MRSA), vancomycin-resistant Enterococcus (VRE), and Carbapenem-resistant Enterobacteriaceae (CRE) present challenges in clinical settings. The limited treatment options for these infections not only compromise patient outcomes but also increase the risk of nosocomial infections and the potential for community spread.

Hence, addressing the antibiotic resistance crisis requires a versatile approach. Phage Therapy has posed as a potential approach towards this global health problem.

Definition, structure, and lifecycle of bacteriophages :

Bacteriophage is a virus which parasitizes a bacterium by infecting it and reproducing inside it. Bacteriophages are much used in genetic research.

The structure of a bacteriophage is as follows :

- Head or Capsid: The head, also referred to as the capsid, is the protein coat that encloses the genetic material of the phage. It is often icosahedral in shape, resembling a geometric polyhedron, but can also have other shapes such as cylindrical or filamentous.
- Genetic Material: Within the head, the genetic material of the phage is contained. This genetic material can be either DNA (double-stranded or single-stranded) or RNA (single-stranded). The DNA or RNA carries the phage's instructions for replication and production of viral components.
- Tail: The tail is a structure that extends from the head and aids in attachment to the bacterial host. It consists of a tail sheath, which contracts during infection, and a tail fiber or tail spike, which interacts with specific receptors on the surface of the host bacterium.
- Baseplate: The baseplate is located at the end of the tail and is involved in the attachment process. It often contains proteins that facilitate the initial contact and recognition of the host bacterium.
- Tail Fibers or Spikes: Tail fibers are filamentous extensions of the tail that play an important role in recognizing and binding to specific receptors on the bacterial cell surface. They enable the phage to attach to the appropriate host and initiate the infection process.
- Enzymes: Bacteriophages may carry enzymes that aid in the infection process. For example, lysozyme enzymes can break down the bacterial cell wall, facilitating entry of the phage's genetic material into the host cell.

General Structure Of A Bacteriophage

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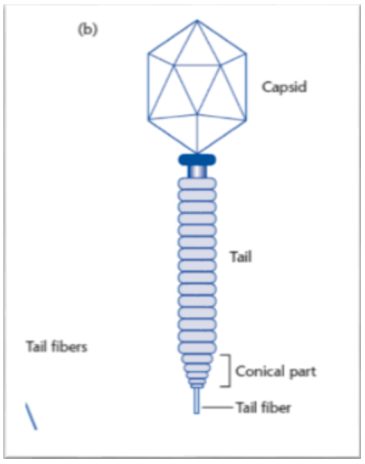


Mechanism of Bacteriophage Infection :

A. Attachment: The initial step in phage infection is the attachment of the phage to the bacterial cell. This attachment is facilitated by tail fibers or similar structures, which bind to specific receptors on the bacterial surface. The type of tail fibers determines the phage's host specificity. Bacterial receptors, such as proteins, lipopolysaccharides (LPS), pili, or lipoproteins, serve other functions in the bacteria but are exploited by phages for infection.

B. Irreversible Binding: After initial attachment, the phage forms a stronger and irreversible bond with the bacterium, typically mediated by components of the base plate. Phages lacking base plates have alternative mechanisms to tightly bind to the bacterial cell.

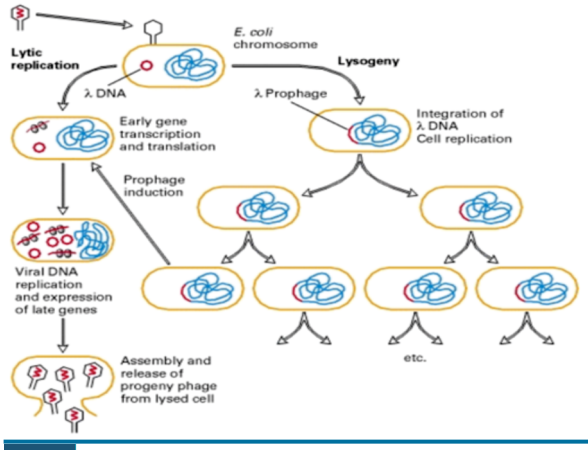
C. Penetration: Following irreversible binding, phages with contractile sheaths undergo sheath contraction, which propels the hollow tail fiber through the bacterial envelope. Phages without contractile sheaths employ other mechanisms to breach the bacterial envelope, often utilizing enzymes to digest bacterial components.

D. Nucleic Acid Delivery: Once the phage enters the bacterial envelope, the nucleic acid contained within the phage head is injected into the bacterial cell. In contrast to animal cell viruses, only the phage's nucleic acid typically enters the bacterial cell, while the rest of the phage remains outside. Some exceptions exist, but generally, bacteria lack the ability to engulf foreign materials.

Lytic And Lysogenic Cycles Of Bacteriophages

Lytic and lysogenic cycles are two distinct life cycles of bacteriophages, also known as phages, which are viruses that infect and replicate within bacterial cells. These cycles represent different strategies employed by phages to propagate and ensure their survival.

In the lytic cycle, the phage infects the bacterial cell, takes over its machinery to replicate, and eventually causes the cell to burst, releasing new phages. This cycle leads to the rapid spread of phages and destruction of the infected bacteria. In the lysogenic cycle, the phage's DNA integrates into the bacterial chromosome, remaining dormant and replicating along with the host.



The lysogenic cycle allows the phage to coexist with the bacterium for a longer time without causing cell lysis. Under certain conditions, the integrated phage DNA can initiate the lytic cycle. These cycles offer different strategies for phage survival and the potential for gene transfer between bacteria.

The ability of phages to switch between these cycles contributes to their adaptability and their impact on bacterial populations and ecosystems.

Advantages Of Bacteriophage Therapy :

Specificity :

Bacteriophages have the remarkable ability to selectively target and infect specific types or strains of bacteria, while leaving non-targeted bacteria unharmed. This targeted approach allows for precise elimination of pathogenic bacteria, minimizing impact on beneficial bacteria.

Broad Range of Action :

Bacteriophages can effectively infect and kill a wide variety of bacterial species, including those that are resistant to antibiotics. They have the ability to recognize and attach to specific receptors on the surface of bacterial cells, enabling efficient infection across different types of bacteria.

Self-Replication :

Bacteriophages are capable of reproducing inside the bacteria they infect, leading to the production of many new phages. This self-replication property allows for a potential amplification of the therapeutic effect, even with a small initial dose of phages.

Adaptive Nature :

Bacteriophages can adapt and evolve along with the bacteria they infect. This ability allows them to respond to changes in bacterial populations, potentially overcoming bacterial resistance mechanisms and evolving new strains with improved infectivity.

Limited Impact On Healthy Bacteria :

Unlike broad-spectrum antibiotics that can disrupt the normal microbial communities in the body, bacteriophages typically target specific pathogens, sparing the beneficial bacteria. This selective action helps to maintain the balance of the body's natural microbiota.

Limitations of Bacteriophage Therapy :

Narrow Host Range :

Bacteriophages typically have a narrow host range, meaning they can only infect and target specific types or strains of bacteria. This limitation necessitates the identification and selection of phages that are effective against the specific bacteria causing the infection. It may require a tailored approach for each patient, which can be time-consuming and resource-intensive.

Development of Phage Resistance :

Bacteria have the potential to develop resistance to bacteriophages over time, similar to the development of antibiotic resistance. As phages replicate within bacterial cells, mutations can occur in the bacterial genome, leading to the emergence of phage-resistant bacterial strains. This resistance can reduce the effectiveness of bacteriophage therapy and limit its long-term success.

Limited Availability And Characterization:

Compared to traditional antibiotics, the accessibility and availability of well-characterized phages may be more limited. Phage isolation, purification, and characterization can be complex and time-consuming processes. Additionally, regulatory frameworks and approval processes for phage-based therapies may vary across different regions, further impacting their availability.

Potential Side Effects and Safety Concerns :

As with any therapeutic approach, there are potential side effects and safety concerns associated with bacteriophage therapy. Although phages are generally considered safe, the possibility of adverse reactions or unintended effects cannot be completely ruled out. Rigorous preclinical and clinical studies are needed to evaluate the safety and potential risks of phage therapy in human subjects.

Limited Understanding And Research :

While bacteriophages have been used for decades in some regions for

therapeutic purposes, there is still much to learn about their mechanisms of action, interactions with the immune system, and long-term effects. Further research is needed to better understand the optimal administration protocols, dosage, and potential combination therapies with antibiotics or other antimicrobial agents.

Bacteriophages As Alternatives To Antibiotics:

Phage therapy, the use of bacteriophages to treat bacterial infections, has a long history that began in 1919 in Paris with the pioneering work of d'Herelle. He successfully treated bacterial dysentery patients using oral phage preparations, resulting in rapid recovery within 24 hours. Subsequently, d'Herelle introduced intravenous (IV) phage therapy for invasive infections. In 1921, Bruynoghe and Maisin published the first report on the use of phages to treat staphylococcal skin disease, demonstrating significant clinical improvements within 24 to 48 hours of phage injection.

In a study by Sivera Marza et al. A successful treatment of a burn patient colonized by Pseudomonas aeruginosa was reported using topical phage application. The patient had previously undergone skin grafts, and months later, P. aeruginosa colonization persisted. To address this, a purified phage preparation was applied to filter paper discs and placed on the colonized burned areas. After three days, further isolation of P. aeruginosa was no longer observed, leading to a successful subsequent grafting procedure. This case demonstrates the potential effectiveness of using phages topically to target specific bacterial infections and highlights their potential role in treating burn-related complications.

Despite the advent of antibiotics, phage therapy remained extensively used in eastern Europe and the former Soviet Union, with the Eliava Institute in Tbilisi, Georgia, serving as a prominent center for phage research and treatment. The resurgence of interest in recent years shows the urgent need for alternative treatments against antibiotic-resistant bacteria, and ongoing clinical trials aim to further explore the potential of phage therapy as a viable therapeutic option.

Potential For Personalized Phage Therapy :

Personalized bacteriophage therapy is an approach that makes use of the power of bacteriophages and customizing them according to our needs. Unlike broad-spectrum antibiotics, which can lead to the emergence of drug-resistant bacteria, bacteriophage therapy offers a targeted and personalized solution. This treatment involves identifying the specific bacteriophages that can effectively kill the infecting bacteria and tailoring the therapy to the individual patient's needs. By exploiting the inherent specificity and adaptability of bacteriophages, personalized bacteriophage therapy holds significant potential in addressing the rising challenge of antibiotic resistance and providing effective treatments for bacterial infections that were once difficult to treat.

A case report describes the utilization of a personalized bacteriophage-based therapeutic approach in the treatment of a 68-year-old diabetic patient with necrotizing pancreatitis and a complicated MDR Acinetobacter baumannii infection. Despite receiving multiple courses of antibiotics and undergoing percutaneous drainage for a pancreatic pseudocyst, the patient's condition continued to deteriorate over a period of four months. With the absence of effective antibiotics, two laboratories identified nine bacteriophages that exhibited lytic activity against the A. baumannii isolate obtained from the patient. Intravenous and percutaneous administration of these bacteriophages into the abscess cavities resulted in a reversal of the patient's clinical decline, clearance of the A. baumannii infection, and a subsequent return to a healthy state.

Combination therapy : Phages and antibiotics

The combination of phages and antibiotics has shown remarkable efficacy in combating bacterial infections. When phages and antibiotics are used together, they synergistically enhance their effectiveness, a phenomenon known as phage-antibiotic synergy (PAS). This synergy is observed when sub-lethal doses of antibiotics are administered to bacteria that are already infected by phages, resulting in significantly larger phage plaques What makes this interaction particularly interesting is that phages can strengthen the effectiveness of existing antibiotics. They can prolong the action of antibiotics and, in some cases, even revive their ability to work against specific strains of bacteria. This promising approach of combining phages with antibiotics offers a novel strategy to overcome bacterial resistance and improve the effectiveness of antibiotic treatments.

Based on a study by Kevin Diallo and Alain Dublanchet, it is evident that the combination of phages and antibiotics demonstrates a synergistic action in combating bacterial infections. The phenomenon of phage-antibiotic synergy (PAS) is observed when sub-lethal doses of antibiotics are administered alongside phage infection, leading to a substantial increase in the size of phage plaques. This synergy holds immense potential for overcoming bacterial resistance and enhancing the effectiveness of antibiotic therapies.

Future Directions and Research Outlooks :

Phage Engineering :

Progress in technologies, such as high-throughput sequencing, genome editing, and synthetic biology has opened doors to phage engineering, which is the process of manipulation and modification of bacteriophages for various purposes including therapeutics , scientific research, and biotechnological advancements. It involves genetic engineering techniques to modify the genome of bacteriophages, such as introducing or deleting specific genes, altering their host range, or enhancing their efficacy against target bacteria. Phage engineering aims to customize and optimize bacteriophages to better suit specific applications such as developing phage therapy to combat infections, creating diagnostic tools, or designing phages for targeted delivery of therapeutic agents. Phage engineering opens up new possibilities for tailoring bacteriophages to address various challenges in medicine, biotechnology, and microbiology.

Phage Therapy Validation :

Clinical trials play a crucial role in evaluating the efficacy and safety of phage therapy. These trials involve administering phage preparations to patients with specific bacterial infections and carefully monitoring their outcomes. Thorough clinical trials are necessary to determine the appropriate dosage, administration route, treatment duration, and potential side effects of phage therapy. They also help identify specific patient populations or infection types that are most likely to benefit from phage therapy.

Moreover, conducting controlled clinical trials allows for a direct comparison of phage therapy with standard treatments or placebo, providing the evidence of its efficacy. Randomized controlled trials (RCTs) are considered the gold standard for assessing the effectiveness of medical interventions, and their implementation in phage therapy research can provide more reliable data on the therapy's clinical benefits.

In addition to clinical trials, further research is needed to address several important aspects of phage therapy. This includes a deeper understanding of the pharmacokinetics and pharmacodynamics of phages, optimal phage selection and characterization, potential interactions with the human immune system, and the development of standardized protocols for phage production, quality control, and delivery.

Strategies to overcome Phage resistance :

Efforts to combat phage resistance are essential to ensure the long-term effectiveness of phage therapy. Several strategies are being explored to overcome phage resistance.

Phage cocktails: Using multiple phages in combination, known as phage cocktails, can increase the chances of infecting and killing bacteria. Phage cocktails target different bacterial strains or employ phages with diverse mechanisms of action, making it harder for bacteria to develop resistance against multiple phages simultaneously.

Phage engineering: Genetic engineering techniques can be employed to modify phages, enhancing their effectiveness against bacteria. This includes modifying phages to target bacterial mechanisms of resistance, increasing their host range, or improving their replication and infection capabilities.

Phage-antibiotic combination therapy: Combining phages with antibiotics can enhance their efficacy and overcome bacterial resistance. Phages can potentiate antibiotics by disrupting bacterial biofilms or synergistically targeting bacteria in conjunction with antibiotics.

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CONCLUSION :

In summary, phage therapy holds significant promise as a targeted approach to combat antibiotic-resistant bacteria. The ability of phages to specifically target and kill bacteria, even those that have developed resistance to antibiotics, makes them a valuable tool in the fight against drug-resistant infections. However, further research and clinical trials are needed to validate the safety, efficacy, and optimal protocols of phage therapy. With continued exploration and advancements in this field, phage therapy has the potential to revolutionize the treatment of antibiotic-resistant bacteria and improve patient outcomes.

REFERENCES :

1. Russell, P.J. (2011). iGenetics: A Molecular Approach (3rd ed.). Benjamin Cummings.
2. Golkar Z., Bagasra O., Pace D.G. (2014). Bacteriophage therapy: A potential solution for the antibiotic resistance crisis. Journal of Infection in Developing Countries, 8(2), 129-136.
3. Schooley, R.T., Biswas, B., Gill, J.J., et al. (2017). Development and use of personalized bacteriophage-based therapeutic cocktails to treat a patient with a disseminated resistant Acinetobacter baumannii infection. Antimicrobial Agents and Chemotherapy, 61(10), e00954-17.
4. Schless RA. 1932. *Staphylococcus aureus* meningitis: treatment with specific bacteriophage. *Am J Dis Child* 44:813–822.
5. Ackermann, H. W. (2009). 5500 Phages examined in the electron microscope. Archives of Virology, 154(2), 185-197.
6. d'Herelle F. 1931. Bacteriophage as a treatment in acute medical and surgical infections. *Bull N Y Acad Med* 7:329–348
7. Ptashne, M., & Gann, A. (2002). Lysogeny and the switch between lysis and lysogeny. In Genes & Signals (pp. 239-262). Cold Spring Harbor Laboratory Press.
8. Hershey, A. D., & Chase, M. (1952). Independent functions of viral protein and nucleic acid in growth of bacteriophage. Journal of General Physiology, 36(1), 39-56.
9. Sulakvelidze, A., & Morris, J. G. (2001). Bacteriophage Therapy. Antimicrobial Agents and Chemotherapy, 45(3), 649-659. doi: 10.1128/AAC.45.3.649-659.2001
10. Pires, D. P., Vilas Boas, D., Sillankorva, S., & Azeredo, J. (2015). Phage Therapy: A Step Forward in the Treatment of Pseudomonas aeruginosa Infections. Journal of Virology, 89(2), 744-752. doi: 10.1128/JVI.02035-14
11. Diallo K, Dublanchet A. Benefits of Combined Phage-Antibiotic Therapy for the Control of Antibiotic-Resistant Bacteria: A Literature Review. Antibiotics (Basel). 2022 Jun 22;11(7):839. doi: 10.3390/antibiotics11070839. PMID: 35884092; PMCID: PMC9311689.