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Bacteriophages – A New Frontier in Medicine

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Abstract

Bacteriophages, or phages, are viruses that specifically target and infect bacteria, offering an innovative alternative to traditional antibiotic treatments, especially in the face of rising antibiotic resistance. The resurgence of phage therapy has been driven by the increasing prevalence of multidrug-resistant bacterial strains and the slowdown in the development of new antibiotics. Phages, unlike antibiotics, target specific bacterial strains, reducing the impact on the natural microbiota and potentially offering safer and more precise treatment. However, the clinical application of bacteriophages presents several challenges. One major issue is bacterial resistance to phages, like antibiotic resistance. Bacteria can evade phages by altering receptors or employing defense mechanisms to block phage DNA injection. Another concern is phage-induced lysis, which may release harmful bacterial toxins into the body. Additionally, phages can transmit genetic material, such as virulence factors or antibiotic resistance genes, to the microbiome, which brings potential safety issues. Another challenge is the immune system's response to bacteriophages, as the body might identify them as foreign agents and remove them before they can perform their intended function. The specificity of phages, while advantageous in reducing harm to non-target bacteria, complicates treatment, requiring personalized phage cocktails tailored to each infection, making standardization and large-scale production difficult. Despite these hurdles, bacteriophage therapy holds significant promise as a complementary or alternative approach to antibiotics, particularly in addressing infections that no longer respond to conventional treatments. Ongoing research and clinical trials are critical to understanding and mitigating the limitations of phage therapy to integrate it successfully into modern medical practice.

Keywords: Virus, bacteriophage, multi-drug-resistant bacteria, bacterial resistance, specificity, phage therapy

INTRODUCTION

Bacteriophages (phages) are bacterial viruses. They are abundant and are present in a diversified manner living on the Earth. Phages are present in the human body (saliva, sputum, blood). They are also found in soil and water. They enter the blood and other tissues through different administration routes. Phages can pass the intestinal barriers and get into the blood, lymph, and internal organs [1].

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Bacteriophages specifically target and destroy bacteria without affecting human or animal cells. As a result, they can be used on their own or alongside antibiotics to treat bacterial infections in patients. In the last 30 years, the situation has changed with the rapid rise of multidrug-resistant bacteria (superbugs) along with the decline in the production of novel antibacterial agents by pharmaceutical companies as the market of antibacterial agent production is less profitable than others. Hence, it is becoming difficult to treat

many life-threatening bacterial infections. Scientists are now considering using bacteriophages to treat these dangerous bacterial infections [2]. Developing therapeutic products that are alternative to antibiotics can be a great help in fighting against antibiotic-resistant bacterial organisms.

Bacteriophage and bacteriophage-based products can become the new best alternative to antibiotics [3].

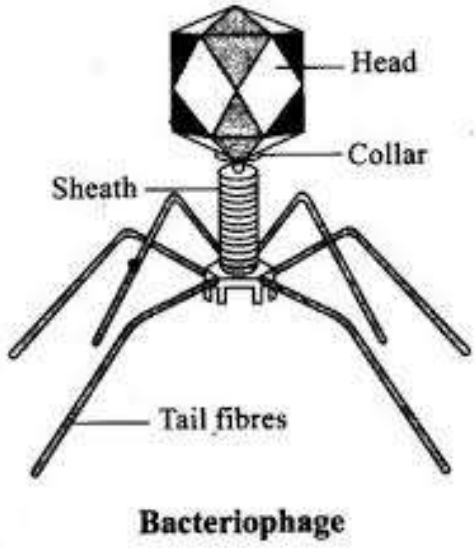

Figure 1. Morphology of bacteriophage.

BIOLOGY OF BACTERIOPHAGE

Bacteriophages (or phages) are stationary viruses that exclusively infect and replicate within bacterial cells. As the most abundant biological entities on Earth, they are constantly found in the environment. Phages come in diverse forms, sizes, and genetic structures. They are made up of a nucleic acid genome enclosed in a capsid protein shell that is encoded by phages. By doing this, the genetic material is shielded and made ready to infect the next host cell. Phages come in a variety of forms, and under an electron microscope, some of them seem to have distinct heads, legs, and tails as seen in Figure 1 [4]. Whenever a bacteriophage attaches to a bacterial cell, it undergoes 1 out of 2 replication cycles, lysogenic or lytic.

Lytic Replication

In the lytic replication process, the bacteriophage binds to a susceptible bacterial host and injects its genome into the host's cytoplasm. It then utilizes the host's ribosomes to synthesize viral proteins. These viral genomes and capsid proteins assemble to create numerous copies of the phage. As the host cell is destroyed, more bacteriophages are produced, which then go on to infect other bacterial cells (Figure 2).

Lysogenic Replication

In the lysogenic replication cycle, the bacteriophage binds to a vulnerable bacterial host and injects its genome into the host's cytoplasm. The viral genome integrates with bacterial genetic material. They are known as prophage. Repeated replication of viral genetic material has no lethal effects on the infected host (Figure 2) [5].

USING BACTERIOPHAGE TO TREAT BACTERIAL INFECTIONS

A study was carried out with 15 healthy participants, who were administered an oral mixture of nine T4-like E. coli strains over a period of two days. After 5 days, even though phages were detected in the feces of almost all the individuals surprisingly, there was no modification of their gut microbiota in those individuals.

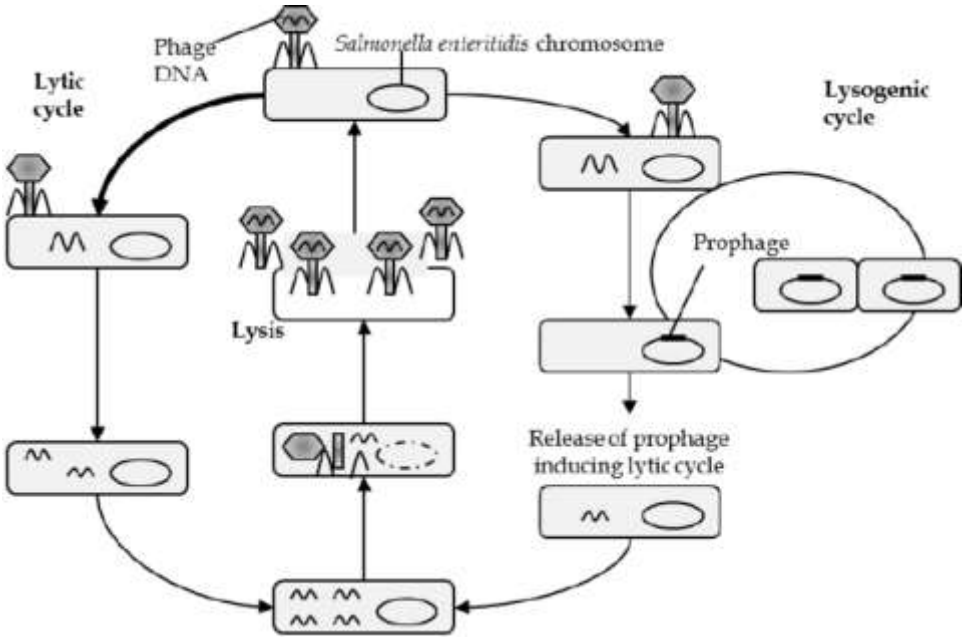

Figure 2. Lytic and lysogenic replication.

Bacteriophages offer several advantages compared to antibiotics. They are safer because they replicate only in the target bacterial cell but cannot infect the mammalian cells. This conclusion has been validated by numerous experiments conducted in Eastern Europe in the past. Many ongoing studies are being conducted on animals and humans and none of them have reported any adverse effects after the administration of bacteriophages [6]. They have come out to be more effective than antibiotics. No antibiotic drug can kill all the bacterial species even though they have a broad spectrum of effects. The most appealing feature of BPs is their specific action, meaning they can target and eliminate only the pathogens they are designed to recognize. Their narrow spectrum of activity addresses a crucial issue associated with antibiotic use by avoiding the disruption of the entire microbiome, preventing the elimination of potentially beneficial bacteria, overgrowth of secondary pathogens, and the development of resistant bacteria [7]. Administration of phages is easier compared to antibiotics as they require repeated administration, unlike bacteriophages. This is because bacteriophages can remain in the human body for several days [8, 9]. Therefore, using bacteriophage to treat bacterial infections might be less expensive compared to antibiotics (Figure 3).

Figure 3. Phages attacking bacteria.

Problems Related to Using BPs for Various Bacterial Infections

Potential concerns with phage therapy include the possibility of genetic material being transferred to the microbiome, such as virulence factors or genes that provide antibiotic resistance; bacteria developing resistance to the bacteriophage; and the increase among of endotoxin due to host cell (bacterial cell) lysis [10]. Before BP can be considered as a potential therapeutic agent, it must be shown to be specific to a particular bacterial strain. This is a complex issue because the evidence of

BP's ability to destroy bacteria can differ depending on the interactions between the BP and the bacterium, as well as how they change over time and the amount of virus used in the test [11].

Bacterial resistance to bacteriophages is highly possible, as bacteria are capable of evolving various mechanisms to defend against viral infections. These mechanisms include hiding, changing structure, or loss of receptors. They can also release substances that can prevent the phages from attaching to bacterial pathogens. These bacterial cells can even block the phage DNA from injecting into them and inhibit phage replication and its release [12]. The development of bacterial resistance to bacteriophages can be reduced by using BP cocktails, administering a higher initial phage inoculum, or combining phage with antibiotics, if phages can kill pathogens faster than they can replicate. Then, a high inoculum is linked to a reduced risk of developing bacteriophage-resistant bacteria. However, these findings indicate that several factors must be considered, such as the bacterial resistance induced by each virus and the amount of the virus required for the development of bacterial resistance [13].

Reduced Activity of BPs Due to Immune System Response

The immune system recognizes bacteriophages and their products as they are non-self-antigens. This can reduce the benefits of Phage administration. Studies have shown that humans and animals have demonstrated different immune responses to phages depending upon the phage strain, route of administration, and their prior exposure [14]. In animals with severe combined immunodeficiency (SCID), BP titters remained stable for a prolonged period, whereas in healthy mice, 99% of BPs were cleared within 60 minutes of injection [15].

CONCLUSIONS

Bacteriophages offer a promising alternative to conventional antibiotics in combating multidrug-resistant bacterial infections. Their unique ability to specifically target and eliminate pathogenic bacteria while sparing beneficial microbiota highlights their potential as a safer therapeutic option. As the medical community grapples with the growing threat of antibiotic resistance, the resurgence of phage therapy offers a glimmer of hope. However, challenges remain, including addressing potential bacterial resistance to phages and the implications of immune responses. Ongoing research and clinical trials are crucial to comprehensively assessing the effectiveness and safety of phage therapy, which could lead to its adoption in contemporary medical treatments. As we venture into this new frontier, bacteriophages may well become a cornerstone of infection management, ultimately transforming our approach to treating bacterial diseases.

In addition to their targeted action, bacteriophages possess several characteristics that make them particularly suitable for therapeutic applications. For instance, they can replicate within the bacterial host, leading to a self-amplifying effect that enhances their efficacy. This is particularly advantageous in treating infections caused by a single bacterial species, where the phage can proliferate at the site of infection, providing a sustained antibacterial effect without the need for high doses. Moreover, bacteriophages can be engineered or selected for their lytic activity, allowing for customization based on the specific bacterial strain involved in an infection.

Phage therapy also presents the possibility of combining with traditional antibiotics. This synergistic approach could enhance treatment outcomes, especially for biofilm-associated infections, which are notoriously difficult to eradicate. Furthermore, the use of phages could help mitigate the adverse effects associated with antibiotics, such as disruption of the gut microbiome, which can lead to secondary infections and complications.

Despite these advantages, several factors must be addressed before phage therapy can be widely implemented. Standardization of phage preparation, the need for regulatory approval, and the development of robust clinical protocols are essential. Additionally, educating healthcare providers and patients about the potential benefits and limitations of phage therapy will be critical to its

acceptance in clinical practice. As research progresses and more data become available, bacteriophages hold the potential to revolutionize our treatment paradigms, offering a viable solution in the fight against antibiotic resistance and improving patient outcomes in bacterial infections.

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