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From enemies to the only hope: viruses as the last chance to fight multidrug resistance

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Streszczenie

Antybiotykooporność to zjawisko nabierania przez bakterie oporności na antybiotyki. Jest ono spowodowane nadmiernym wykorzystywaniem antybiotyków w medycynie, ale także w rolnictwie czy przemyśle. Z uwagi na rosnący problem oporności na antybiotyki niezbędne jest nowatorskie podejście do problemu. Jedną z możliwości jest zastosowanie bakteriofagów (wirusów atakujących bakterie) w celu kuracji chorób bakteryjnych. W artykule przedstawione zostaną najważniejsze kwestie związane z tym tematem, takie jak: cykl replikacyjny bakteriofagów, zalety i wady terapii fagowej oraz powody, dla których nie jest ona powszechnie stosowana.

Abstract

Antibiotic resistance is the phenomenon in which bacteria become resistant to antibiotics. It is caused by the excessive use of antibiotics in medicine, as well as in agriculture and industry. Due to the growing problem of antibiotic resistance, an innovative approach to the problem is necessary. One possibility is the use of bacteriophages (viruses that attack bacteria) to treat bacterial diseases. The article will present the most important issues related to this topic, such as the bacteriophage replication cycle, the advantages and disadvantages of phage therapy, and the reasons why it is not widely used.

Introduction

Imagine a drug that is self-replicating, cheap, accurate, safe for human cells, and able to evolve in response to bacterial evolution. It is believed that such therapeutics are present only in science fiction movies whilst we have them at our fingertips (literally!).

Bacteriophages (phages) are viruses that infect and replicate with extremely high accuracy within only bacterial cells. They occur wherever they can find bacteria to attack. Therefore, they can be found on the skin, in soil, in sewage, in the sea, in the digestive tracts of animals and humans, and in food. They do not have a cellular structure, and their viability is widely questioned by scientists which is why they are not called "organisms." Considering their molecular structure, they are just particles of proteins and nucleic acid which can be double or single stranded RNA or DNA surrounded by protein capsid (Naureen *et al.* 2020).

Bacteriophages are now available in some types of industry, for example Listex™ P100 used to combat *Listeria monocytogenes* in food products (e.g. ready meals, cheeses) to increase food safety (Heshmati *et al.* 2021). Another example is Staphefekt® which is a preparation applied in dermatology in the treatment of acne and chronic skin infections caused by *Staphylococcus aureus* (Totté *et al.* 2017). Bacteriophages have therapeutic potential for diseases caused by antibiotic-resistant bacteria. An example is the drug *Phago-Staph Bacteriophage* (Eliava BioPreparations, Tbilisi, Georgia), which is used to combat strains of *S. aureus*. It can be used for urogenital infections, enteric infections, purulent-septic infections in newborn, surgical infections, airways infections and other *Staphylococcal* infections [1].

Phage therapy is currently available only for experimental use in patients for whom conventional treatments (such as antibiotics) have no therapeutic effect. But why phage therapy is not applicable and widely used? The following part of the paper is devoted to a further consideration of this problem.

Lytic cycle vs lysogenic cycle

A key aspect of bacteriophage biology is how they replicate using bacterial cells, which occurs through one of two basic cycles: lytic or lysogenic (Fig. 1). Comprehending the lytic and lysogenic cycles is crucial to understand the interactions between phages and bacteria and the potential use of phages in antimicrobial therapy.

During the lytic cycle bacteriophage attacks the bacterium, injects its DNA or RNA and the host cell starts to replicate the genetic material of bacteriophage. As the result of which there are many of fragments of new bacteriophages inside a single bacterium and the cell "explodes" releasing newly assembled bacteriophages that can attack new bacteria cells.

The lysogenic cycle begins in the same way as the lytic one, but after the injection of genetic material, inside the cell, it is not copied immediately, instead, it is recombined with a specific fragment of the bacterial chromosome. As a result, genetic material is integrated with the bacterium's genetic material, called prophage. It can passively replicate as DNA during cell division since it is integrated into the host bacterium's genome and transition from the lysogenic to the lytic cycle.

Nowadays, bacteriophages are used in a process called transduction. It happens when some part of genetic material of the bacterium is encapsidated by a newly created phage. This material is then transferred to another bacterium that is attacked by the phage and may be recombined into a chromosome or plasmid (Chiang *et al.* 2019). This

process, called horizontal gene transfer allows bacteria to acquire new features (such as antibiotic resistance genes). This machinery is used in genetic engineering and biotechnology to produce proteins of industrial or pharmaceutical importance, modify bacterial metabolism to optimize fermentation processes and create modified bacterial strains used in bioproduction or bioremediation.

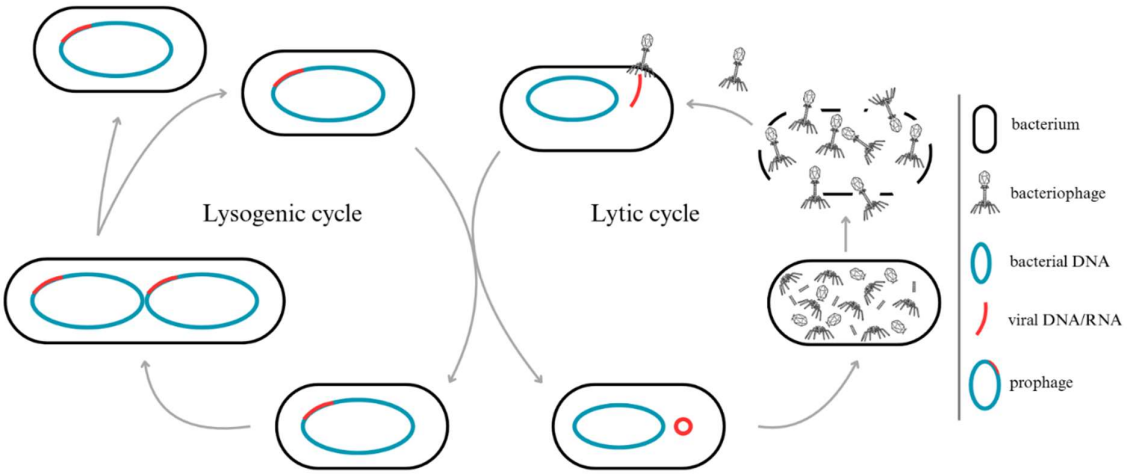

Fig. 1 Diagram of the bacteriophage replication cycle in bacteria.
Figure created by the author based on [2]

Advantages of bacteriophages' using

One of the mechanisms used by bacteria to cause human' chronic infections is biofilm formation (Leid *et al.* 2002). According to the results of research conducted in this area, phage-antibiotic synergy (PAS) used in the treatment of biofilms is more effective than using only phages or antibiotics. It is caused by their mechanisms of action that are complementing each other. Phages can be more effective when the biofilm is covered with a polysaccharide layer, which antibiotics usually cannot overcome (Xu *et al.* 2024).

Bacteriophages multiply within bacterial cells which leads to an increase in their number in a specific area. Additionally, after cell lysis, the newly assembled bacteriophages attack adjacent bacteria, causing the biofilm to degrade and its regenerative capacity to decrease. Moreover, phage-derived depolymerases break down the extracellular matrix, allowing phage particles to effectively penetrate the biofilm structure and infect deeper located bacteria (Stobnicka-Kupiec 2024).

Antibiotics cause many negative changes in the intestinal microbiota, such as a reduction in the diversity of bacteria or a decrease in the production of functionally diverse proteins engaged in crucial physiological processes (Langdon *et al.* 2016). Referring to the remarkable specificity of bacteriophages (Duckworth, Gulig 2002), it can be concluded that the side effects of phage therapy will be reduced (Fernández *et al.* 2019). Moreover, research shows that the risk of bacterial resistance is lower than when using antibiotics (Carlton 1999). The high accuracy of phages is also a big advantage compared to the broad spectrum of action of antibiotics, which also kill symbiotic bacteria (Zhang, Chen 2019). This opens new possibilities for effective treatment of patients without causing damage to their microbiota (Fig. 2).

One of the biggest benefits in the case of bacteriophages' usage is their property to replicate *in vivo*, therefore it is achievable to apply a lower therapeutic dose because the concentration of the drug amplifies itself (Saha, Mukherjee 2019). Furthermore, phages can be isolated from samples taken from recovering patients, cultivated, and used in the treatment of patients infected with the same strain of bacteria (Hyman 2019). Accordingly, obtaining bacteriophages is much easier than making it from scratch. Throughout history phages have been administered by various routes: orally, rectally, locally, as aerosols or intrapleural injections, and intravenously (Sulakvelidze *et al.* 2001).

The literature also describes a modern approach using bacteriophages to combat drug-resistant bacteria using the phage-vectored CRISPR-Cas9 system. It is a modern genetic engineering tool that allows precise genome editing by targeted cutting and modifying specific DNA sequences. This method enables the removal of antibiotic resistance genes or the destruction of key fragments of bacterial DNA (Balcha, Neja 2023).

Growing antibiotic resistance is currently one of the biggest public health problems. It causes about seven hundred thousand deaths per year (2016 data), and if the growing trend continues, this number will increase to ten million by 2050 (O'Neill 2016). The consequences of using antibiotics too often and widely (especially broad-spectrum antibiotics) can be devastating for society. Antibiotic resistance may not seem like a big problem nowadays, but over the years it can be one of the leading causes of death. It is worth focusing on alternative ways of treating bacterial infections, such as bacteriophages.

	Antibiotics	**Bacteriophages**
Specificity	broad-spectrum/narrow-spectrum	very specific
Resistance	increasing resistance	possible resistance but easy to overcome
Effect on microbiota	kill symbiotic bacteria	attack only targeted bacteria
Possibility of modification	limited	possibility of genetic engineering

Fig. 2. Comparison of the properties of antibiotics and bacteriophages in the context of the treatment of bacterial diseases. Figure created by the author.

Where does antibiotic resistance come from?

Prescribing antibiotics as drugs for every ailment creates selective pressure on bacteria (primarily those present in our bodies) and results in the creation of so-called "superbugs." A factor that deserves special attention is broad-spectrum antibiotics, which kill a wide range of bacteria. As a result, antibiotic-susceptible bacteria (which there are many in the case of broad-spectrum antibiotics) can mutate and become resistant to multiple antibiotics from the same class.

Excessive use of antibiotics in animal husbandry (to limit the spread of diseases, prevent infections and produce more meat at a lower cost) leads directly to the occurrence of drug-resistant pathogens not only in animals and animal products, but also among people in their environment (farmers and people working on the farm) (Paulson, Zaoutis 2015).

The other side of the coin

The aforementioned arguments offer significant potential. The question is then why bacteriophages are not widely used in disease therapy nowadays? There are a few factors that need to be considered.

Bacteriophages were discovered twice, separately by different scientists – Frederick Twort in 1915 and Félix d'Hérelle in 1917 (Carlton 1999). After the second one, the finder suggested that phages can be used as a therapeutic tool, and bacterial infections started to be treated by bacteriophage therapy. G. Eliava Institute of Bacteriophages at Tbilisi has become one of the main research centres in the field of the above-mentioned treatment.

After World War II and antibiotics discovery – they seemed to be the perfect way to fight bacterial diseases. Because of the Eastern/Western confrontation at that time, the Eastern Bloc had no opportunity to use antibiotics, which resulted in extensive exploration and analysis of bacteriophages' therapeutic properties. All the research had its center at the Eliava Institute of Bacteriophage, Microbiology, and Virology of the Georgian Academy of Sciences, Tbilisi, Georgia, and the Hirszfeld Institute of Immunology and Experimental Therapy of the Polish Academy of Sciences, Wroclaw, Poland (Sulakvelidze *et al.* 2001). After discovery of antibiotics the research concentrated on them due to their properties such as fast synthesis and a wide spectrum of activity (which, as we know nowadays, is both an advantage and a disadvantage). Bacteriophages were forgotten because antibiotics were the simplest and most effective way to treat bacterial infections. Moreover, it was not realized that antibiotic resistance would be such a big problem a century later.

The high specificity of the phages is not only an advantage. Clinics would have to create different phage cocktails for people suffering from even the same disease because it can be caused by different strains of bacteria. This may increase the time the patient has to wait for the drug to be administered which is additionally prolonged by the complicated diagnosis process.

One of the more complicated aspects is the issue of patents, which in the case of natural entities is extremely problematic. This makes phage therapy research unprofitable for private pharmaceutical companies that want to reserve the exclusive right over the "invention."

Summary

Public perception of viruses is mostly negative. Should it be the determinant of whether to use phage therapy? Of course not, but the

negative point of view according to which viruses are the "enemies of life" will definitely play a role in the aversion of appliance phage therapy for general use (Verbeken *et al.* 2007). Our task now is to raise awareness not only about bacteriophages but also about science in its broad sense and the laws that govern nature.

Even though, the properties of bacteriophages such as specificity, safety and effectiveness are very promising, I think, a utopian vision of "a perfect cure" is not distant from us. It is unreachable. Why? Because perfection does not exist. The concept of the idealistic world can be present only in movies or advertisements. Should it keep us from researching and trying to be point-device scientists? Surely not, but we must accept, that we are far from perfection, and we should search for the best possible, not ideal cure. It is high time to think seriously about antibiotic resistance and its potentially devastating consequences. Right now, one of the best options is phage therapy, which can play a crucial role in our lives within the next several dozen years.

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Notka o autorce: *Studentka I roku studiów magisterskich biotechnologii na MWB UG i GUMed. Oprócz bakteriofagów i szczepionek interesuje ją kryminalistyka, a szczególnie wykorzystanie nauki w rozwiązywaniu spraw kryminalnych. W wolnym czasie czyta thrillery psychologiczne i słucha podcastów true crime.*