Review Article

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Revolutionizing the fight against multidrug-resistant bacteria: Phage and phage products as the leading armament in future: Review

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ABSTRACT

The prevalence of bacteria that have developed resistance to multiple antibiotics has increased in recent years, posing a serious threat to public health. Some of these strains have proven almost immune to frequently used antibiotics. Methicillin-resistant *Staphylococcus aureus* (MRSA), for instance, is an example of a strain of bacteria that has become resistant to multiple medications. The World Health Organization (WHO) has released a report detailing the antibiotic-resistant diseases for which new and potent treatments are urgently needed. There has been a rise in interest in the potential applications of bacteriophage viruses that specifically target bacteria and eradicate them. Since they lack a metabolic system, these viruses must rely on bacteria for reproduction. It is estimated that bacteriophages are about 3 billion years old, making them one of the oldest and most common creatures on Earth. They are essential for keeping germs in check in circumstances where they naturally occur, such as in natural, unprocessed foods. The potential of bacteriophages to improve food safety is one area of increasing interest. Researchers employ animal models, such as invertebrate and vertebrate models, to examine the efficacy of medicines more swiftly and economically than human trials. The zebrafish is one example of a new model that could be used to investigate host-pathogen interactions in the future. Bacteriophage mixtures are being used by scientists as a means of more precisely treating specific infections and slowing the spread of antibiotic resistance.

Introduction

Bacteria resistant to three or more different kinds of antimicrobial medications are known as multidrug-resistant (MDR) bacteria (Magiorakos *et al*., 2012). Gram-positive, Gram-negative, and other (acid-stain) bacteria are the three main subtypes of MDR bacteria. To describe the various forms of resistance identified in healthcare-associated, antimicrobial-resistant bacteria, the terms multidrug-resistant (MDR), extensively drug-resistant (XDR), and pan-drug-resistant (PDR) microorganisms are used variously in the medical field (Aliberti *et al*., 2013).

The European Centre for Disease Prevention and Control (ECDC) and the Centers for Disease Control and Prevention (CDC) are working together to develop a common international terminology to describe acquired resistance profiles in the bacteria *Staphylococcus aureus*, *Enterococcus spp., Enterobacteriaceae* (apart from *Shigella* and *Salmonella*), *Pseudomonas aeruginosa*, and *Acinetobacter* spp. Worked together. Epidemiologically important antimicrobial categories were developed for each bacterium (Wright and Sutherland, 2007). These bacteria use a variety of modifications to prevent or lessen the harm caused by antimicrobials. Multidrug resistance is particularly prevalent today in new infections. Common pathogens include *Staphylococcus aureus* and *Mycobacterium tuberculosis*, as well as *Acinetobacter baumannii* (Nikaido, 2009).

There are two methods by which bacteria might become resistant to many drugs. First, several genes that code for resistance to different medications may be present in each of these bacteria's cells (Lencastre *et al*., 2007). This accumulation frequently occurs on-resistance (R) plasmids. Second, multidrug resistance may arise from elevated gene expression for multidrug efflux pumps, which expel a range of medications (Krishnamoorthy *et al*., 2019).

The use of antibiotics has significantly increased as a result of greater access to modern treatment. Since antibiotics are widely used, the evolution of antimicrobial resistance factors is now outpacing the development of new medications. After penicillin was discovered in 1928, a large number of other antibiotics were also found and produced commercially. We now believe that any infectious disease can be treated with antibiotics. Antibiotics are projected to be produced in 100,000 tons annually worldwide, and their use has significantly impacted the ability of bacteria to survive on Earth. The number of pathogen strains resistant to one or more antibiotics, and in certain situations, multiple antibiotics and chemotherapeutic medicines has increased due to the issue of multidrug resistance (Fletcher, 2015).

Tetracycline, chloramphenicol, aminoglycosides, macrolides, and lincosamides are frequently ineffective against MRSA. Transferable vancomycin resistance is currently rather common in Enterococcus and eventually found its way to MRSA in 2002, even though these strains are still uncommon. These strains are also resistant to disinfectants, and MRSA can contribute significantly to the spread of infections in medical facilities. Vancomycin, an antiquated medication, has been reintroduced to treat MRSA infections (Clinical and Laboratory Standards Institute, 2014).

Antibiotic resistance poses a persistent threat to the healthcare sector. New antibiotics and therapy strategies are needed to address this problem. Advances in the identification of novel sources of natural materials containing antibiotics and the growing diversity of antibiotic compounds are yielding chemical clues for novel pharmaceuticals. On the other hand, orthogonal techniques that produce novel chemicals that can extend the shelf life of current antibiotics also inhibit microbial virulence and resistance processes. It is possible to address the problems caused by antibiotic resistance in the twenty-first century because of this new chemistry and our growing comprehension of its causes, processes and spread (Schneider, 2021).

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Bacteriophages assist in preserving bacterial homeostasis, which regulates bacterial growth, in the natural world. But owing to modern technology, we can now comprehend and make use of this resource from nature. Phages have no effect on beneficial microbes in food, commensals in the gastrointestinal tract, or the surrounding bacterial flora in the environment (Hagens *et al*., 2008).

Phages have no effect on the organoleptic properties (taste, structure, color, and aroma) of food items; rather, they are common human and animal commensals. Additionally, they don't negatively impact the environment. Phage levels regularly approach 107/mL and sporadically surpass this value 300-fold due to the prevalence of bacteria in freshwater and marine environments (Hagens *et al*., 2008; Fuhrman,1999; Otawa *et al*., 2007). There are very few truly sterile foods. As a result, phages are probably prevalent because bacteria are present in most of the food that is consumed (Otawa *et al*., 2007).

The fundamental blocks of phage structure are amino acids and nucleic acids, which decompose into a polyhedral head, a short collar, and a helical tail. Head: Double-stranded DNA is present in each of the 2000 capsomeres that make up the head. Tail: The tail consists of a hollow inner tube surrounded by a 24-annular ringed contractile sheath (Filippini *et al*., 2006).

Bacteriophage history

Bacteriophages, which means "bacteria eaters" in Greek, were identified about a century ago. Both Felix d'Herrelle and Edward Twort published separate accounts of isolating filterable organisms that could kill bacterial cultures and create little cleared zones on bacterial lawns. While they both received credit for the discovery, d'Herrelle is credited for naming the organisms "bacteriophages" and dedicating his entire life to researching them, including their potential use in medicine (Ackermann and DuBow, 1987). Naturally occurring bacteriophages, or phages, are the most common microorganisms in our surroundings and can be found in a variety of foods and beverages. Phages are exclusive to a single bacterium and are unable to adhere to other bacteria. They have no influence on people, animals, or vegetation. For countless millennia, humans have been routinely exposed to large amounts of phages through food, drink, and the environment without experiencing any adverse consequences. In aquatic environments, there can be up to 1 billion phages/mL, and in some food products, there can be 100 million phages/g (Hagens and Offerhaus, 2008).

Bacteriophage structure and the mode of phage action inside the host

Every bacteriophage possesses genetic content, which can be either DNA or RNA. These nucleic acids are enclosed in a protein structure. Bacteriophages also have tails and other support structures to link to the surface of the bacteria they attack (Kasman and Porter, 2020).

These phage/host systems have developed into a duo over millions of years, and Figure 1 depicts their optimum shape. A non-specialized immigrant phage would be useless because every bacterium already has a complement of specialized phages with which to compete (Delbrück, 1940).

There are different cycles of phage entry according to phage nature

In general, the first attachment can be reversed because the cell might not be alive at that moment, making it useless to attach. The phage DNA circularizes after the second attachment stage, which is irreversible, and the bacterium begins to produce phage proteins. The entire host cell is sequestered by these proteins, which force the organism to only create new phages. Following progeny phage assembly, two distinct phage proteins cause cell lysis, releasing daughter phages that are prepared to begin the subsequent cycle, each phase of the process necessitates compatibility between the phage and host systems, which accounts for the exceptionally high specificity of phages for a particular host (Abedon, 2008; Los *et al*., 2010; Sime *et al*., 2019).

Lysogenic cycle

Since temperate phages incorporate their genome into the host chromosome or occasionally hold it as a plasmid to be passed on to daughter cells during cell division or horizontally across the bacterial community, they are not used therapeutically. They might go through a normal lytic cycle or lysogenization (Hobbs *et al*., 2016).

When the host circumstances are disturbed, perhaps due to insufficient nourishment, temperate phages begin the lytic life cycle (Hobbs *et al*., 2016). At this moment, prophages become active. At this point, the bacterial cell lyses due to the reproductive cycle as the bacterium develops throughout. The virus multiplies continuously and is present in every bacterial progeny throughout the lysogenic life cycle. One example of a phage having a lysogenic cycle is Phage lambda, which is found in the bacterial virus Escherichia coli (E. coli) (Chen *et al*., 2020).

The wild form of this virus has a mild life cycle that enables it to either live inside its host's genome through lysogeny or enter a lytic phase in which it kills and lyses the cell to produce progeny. Because of certain site mutations, lambda strains multiply before entering the lytic cycle, preventing them from lysogenizing cells. The lambda phage cannot 'push' its DNA through a bacterial cell membrane during an infection because it lacks a contractile tail. Instead, because it has evolved the tip of its tail to interact with a specific pore to allow passage of its DNA to the hosts, it must use an already-existing pathway to enter the host cell (Werts *et al*., 1994).

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For conclusion the step of lambda phage entry as example of Temperate phage

An E. Coli cell is bound by the lambda bacteriophage tail tip J protein. The J protein interacts with the maltose outer membrane porin, an E. coli porin molecule produced by the lamB gene and a portion of the maltose operon (Erni *et al*., 1987). 1) The outer membrane is used to inject the linear phage genome. 2) The mannose permease complex processes the DNA at the 12-base G-C-rich cohesive "sticky ends" of the cos sites, which are encoded by the man XYZ genes and were used to quickly circularize the inner membrane (Xueli *et al*., 2019). 3) The host DNA ligase connects the ends of the viral single-strand DNA. Most people don't know that the first direct nucleotide sequencing of a biological DNA was done on the 12 bp lambda cohesive ends (Casjens and Hendrix 2015; Katsura, 1983).

Lytic phage

Adsorption: During adsorption, one bacteriophage at a time clings to the surface of a bacterial host. Due to the exact connections between the tail and receptors, many bacteriophages only target one specific type of bacterium by attaching itself to the target bacteria's surface receptors.
Penetration: The bacteriophage on the surface of the bacterial cell penetrates the cell membrane during penetration. It does this by dissolving the bacterial cell wall with certain enzymes. The genetic material of the bacterial cell is then incorporated into the bacteriophage.
Transcription: The bacteriophage utilizes the machinery present in each particular bacterial cell during transcription. It reproduces its genetic material and other necessary proteins using the bacterial cell.

Biosynthesis: Phage DNA replicates within the cell, synthesizing new proteins and phage DNA.

Maturation: Completely formed viral phages with a head, tail, and tail fibers are created when the duplicated material combines (Rakhuba *et al*., 2010). The lytic phage entrance stage.

The different way of lytic phage entry

Lytic phages solely employ endolysins

Endolysins can access the glycoproteins within the bacterial cytoplasm when holins break through the cytoplasm. Holin-endolysin synchronization with the late stage of viral replication is achieved via holin-controlled timing of endolysin access to bacterial murein. The synergistic holin-endolysin system is utilized to lyse cells and release mature lytic phage offspring. Lytic phages, which only employ VALs, break down bacterial cell walls early in an infection by means of depolymerases that are attached to the virion particle. Depolymerases are in charge of dissolving polysaccharide molecules such as capsules, lipopolysaccharide (LPS), or biofilm matrix, whereas VALs are in charge of breaking down PG, which is necessary for injecting phage genetic material into the infected host cell (White *et al*., 2011). As holins and endolysins are able to disrupt bacterial cell walls and membranes, lytic phages may be a new weapon in the fight against bacterial infections. They work well against bacteria that are both vulnerable to and resistant to medicines because of this property (White *et al*., 2011).

The lytic phage only injects the DNA that is part of the phage by its tails.

The stages of infection where phage genetic material needs to be delivered into the host cell. To do this, the phage must enter the bacterial cell. There is proof that the tailed phage's baseplate coordinates penetration and adhesion. While phage tails come in a variety of forms in nature, the most developed ones have a genetic material-carrying tube encased in a contractile sheath (Drulis *et al*., 2015) the sheath contracts like a coiled spring and then releases, forcing the tube inside the bacterial cell. The T4 phage's baseplate-tail-tube complex contains around one million atoms overall and is made up of 145 chains made of 15 distinct proteins. The empty phage cell is called the doughnut or ghost that the bacteria take out (Campbell, 1988).

Early endonucleases and exonucleases produced by the lytic phage break down the host DNA

The phage breaks down DNA by producing endonucleases and exonucleases as soon as it enters the host. They can then produce offspring by ynthesizing proteins using the machinery of the host cell. The nucleotides produced can either be removed from the host cell by the T5 phage or recycled by the phage (like the T7 phage) for the replication of their own progeny. The T4 phage, for example, uses chemical modification of the viral cytidines to prevent self-degradation during the process of enabling the phage genome to be separated from the host genome (Nelson *et al*., 2012). The replication of the phage genome requires extra early proteins. Inhibitors produced by the phage may also inhibit the host RNA polymerase. Given that RNA is not when the phage is broken down, it can also produce inhibitors, which prevent the host RNA polymerase from interfering with the viral polymerases in a subsequent infection. The recently synthesized phage genome produces late proteins, including the capsid's tail and components. This procedure might occur minutes after the bacterium is inoculated (Schmelcher *et al*., 2012).

Depending on how urgently new antibiotics are needed to treat each pathogen, the pathogens have been grouped into three priority categories: critical, high, and medium. Bacteria that have developed resistance to numerous medicines, including the carbapenems, a last-resort antibiotic class, are pathogens with a significant need for new antibiotics (Rodríguez *et al*., 2013). Pathogens in the second and third groups contain additional bacteria that are developing an increasing level of antibiotic resistance and are responsible for more widespread illnesses, including gonorrhea and salmonellosis (Latka *et al*., 2017).

Examples Gram-positive MDR bacteria

Staphylococcus aureus

The "golden cluster seed," which is also a spherical bacterium, is typically found in people's skin, intestines, vagina, nose, and throat. Because of the wide range of deadly illnesses it can cause and its quick adaptation to shifting environmental conditions, it is a virus that should be taken much more seriously. Because of these characteristics, treating *S. aureus* infections has become increasingly difficult because of how quickly the bacteria become resistant to standard antimicrobial medications (Weems, 2001; Lowy, 2003).

Methicillin-resistant *S. aureus* (MRSA) infections are a particular health issue when treating staphylococcal infections because of the widespread use of antimicrobial drugs and the transmission of a significant portion of the organism by person-to-person interactions (Chamber, 2005). Therefore, controlling the use of antibiotics and preventing the spread of these strains are essential to the total eradication of this infectious organism. The significance of fecal-oral transmission in humans is highlighted by the fact that the stomach is an essential habitat for parasites and bacteria that can be spread by objects contaminated with feces. It has been acknowledged that stool-borne Staphylococci are a significant pathogen that affects people and causes diarrhea linked to antibiotic use (Weems, 2001; Chamber, 2005).

Prior research compared, categorized, and categorized *S. aureus* phages based on their responses to polyclonal antiserum, which has the ability to halt phage infection. Phage neutralization trials yielded six serogroups, which were used to classify the phages (Okeke, and amikanra, 2003). Eleven distinct staphylococcal serogroups (A-H and J-L) have been identified with the aid of additional staphylococcal phage isolates and sera (Rippon, 1952; Sweere *et al*., 2019). Group E, J, and K phages were demonstrated to favor coagulase-negative staphylococci and to be non-virulent to *S. aureus*. Serogroups A, B, and F comprise most of the temperate phages that infect *S. aureus*.

Types of phages infect Staphylococcus aureus

Herelleviridae family and genus Silviavirus phages

The ranges of the genomes' coverage and identification rates were 85% to 94% and 97% to 99%, respectively. KSAP11 has a small neck typical of *Myoviridae*-presenting phages (Rippon, 1956; Hsieh *et al*., 2011).

With an average head diameter of 93 nm, a tail length of 210 nm, and a tail breadth of 22 nm, the stretched contractile tail, as seen in Figure 8, demonstrates how comparable in size the phage is to Remus (Vandersteegen *et al*., 2013). These features particularly correspond with those of other identified *Herelleviridae S. aureus* phages (Klumpp *et al*., 2010).

Caudovirales phages

A complex virion structure that consists of a head and a long, contractile tail is lytic on *S. aureus* by necessity and is unable to transmit bacterial DNA (Barylski *et al*., 2020). Some are less prevalent and have a short tail; there are only 14 isolates with sequenced genomes. They are members of the *Picovirinae* subfamily of the *Podoviridae* family. Despite being found in a variety of topographical places, phages that infect *S. aureus* are quite similar (Gozdek etal., 2018) and have been connected to the Rosenblumvirus genus, subfamily *Picovirinae* (Glowacka etal., 2019).

Staphylococcus phage PT1028, Staphylococcus phage P954, Staphylococcus phage ROSA, and Staphylococcus phage PT1028

The dsDNA genome size of these *Staphylococcus aureus* phages is 40 kbp or less. They are closely related to multiple additional phages that were recovered from the same host and shared a similar genomic size. A similar viral morphotype with isometric heads and long, non-contractile tails is shown in Figure 10, although P954 and ROSA's morphology is unknown. These phages and their relatives are most likely members of the Siphoviridae family. *Staphylococcus* phage PT1028 is a *Staphylococcus aureus* phage that has little in common with other phages. Its dsDNA genome is just about 20 kbp in size, and its shape is unknown (Kim and Myung, 2012).

Romulus and Remus

It is determined that these phages are members of the *Myoviridae* family. The phages have a contractile tail that is 204 nm long and 17 nm wide, and an isometric head that is 90 nm in diameter. These traits are comparable to those of other viruses that infect *S. aureus*. Consequently, it is probable that the phage SA11, associated with Romulus and Remus, was mislabeled as a siphovirus (Klumpp *et al*., 2010; Lavigne *et al*., 2009).

Twortlike virus-infected phages: appear to be related in terms of genotype and proteome, and their double-stranded genomes range consist of 183 to 217 open reading frames (ORFs), range in size from 127,188 to 140,194 bp, and have a G+C composition of 30.04 to 30.60% (Klumpp *et al*., 2010).

Conclusion

Multidrug-resistant (MDR) bacteria are resistant to at least three different groups of antimicrobial drugs. Antimicrobial resistance factors have increased as a result of antibiotic use, and this trend is rapidly outpacing the development of new medications. Phage therapy was first used a century ago, but due to the sharp increase in bacterial antibiotic resistance, which has led to high rates of illness, death, and cost burden, it has recently gained popularity once more.

Conflict of interest

The authors declare that they have no conflict of interest.

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