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USING THE POTENTIAL OF MYCOBACTERIOPHAGES TO COMBAT TUBERCULOSIS: FROM CRISIS TO CURE

Abstract. Mycobacterium tuberculosis (Mtb) is an intracellular pathogen that primarily affecting the lungs and causing tuberculosis (TB), a fatal and highly destructive illness that poses a vitally important global disease burden. In addition, Mtb can infect any organ in the body, causing other lethal diseases such as tuberculous meningitis, tuberculoma miliary TB, tuberculous abscess, tuberculous encephalopathy, and even intracranial hemorrhage [1]. TB is recognized as a significant global health concern, graded by the World Health Organization (WHO) as the 10th cause of death worldwide .

Key words: Mycobacterium tuberculosis, diagnosing, propertie, bioengineering field

Mycobacteriophages are viruses that infect Mycobacterium spp., including M. smegmatis and Mtb. In this review, we discuss mycobacteriophages in terms of their properties, utility in diagnosing and treating TB, and the advantages and limitations of their use. We also cover how bacteriophages and their encoded structure proteins have been exploited in human health, focusing on recent studies of mycobacteriophages in Mycobacterium spp. and recently developed tools for using these viruses to diagnose and treat the diseases caused by infection with Mycobacterium spp. The cell wall of Mycobacterium spp. is distinguished by its complexity. It comprising of a rich layer of mycolic acid that is covalently linked to an arabinogalactan layer, containing long-chain fatty acids with interjecting glycolipids and phospholipids. The genomes of mycobacteriophages encode lytic enzymes, namely endolysins, which are essential for disrupting mycobacterial membranes to release the newly produced viruses. Based on the capability to produce one or two endolysins, mycobacteriophages are divided into three categories: Lysin A (LysA), Lysin B (LysB), and LysA combined with LysB. LysB is specific and encoded by most mycobacteriophages, whereas LysA is present in the genomes of all bacteriophages, including mycobacteriophages.[2] There are two modular structures of endolysins obtained from phages that infect Gram-positive bacteria: an N-terminal catalytic domain (CD) linked by a flexible bond to a C-terminal cell wall-binding domain (CBD) In Gram-positive bacteria, the N-terminal CD of phage-encoded endolysin is primarily responsible for hydrolyzing distinct peptidoglycan linkages, whereas the C-terminal CBD is essential for non-covalently anchoring the CD to various ligands, typically carbohydrates, within the cell wall, thereby properly fixing the CD in place. Even though the C-terminal CBD is necessary to retain the full lytic activity of the CD, truncating or deleting the CBD can also affect the lyric activity of the mutants. The moment of lysis in the host cell is controlled by a transmembrane channel protein called Holin. Bacteriophage-encoded enzymes also represent a promising class of antibiotics called enzybiotics, which are non-manufactured proteins. [3] While a few reports have shown endolysins to be selective at the serovar level, phage-encoded lytic enzymes often exhibit wider specificity at the genus or species level. This property could lead to great therapeutic options for both acute and chronic infections. Furthermore, endolysins are fast-acting, effective, safe, and highly specific; they have the ability to weaken biofilms and have a low prospect of induced resistance development.[4] Additionally, endolysins can be used either in synergy with antibiotics or alone. Rapid detection and evaluation of Mtb resistance are made

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possible by the nucleic acid amplification approach, which uses nucleic acid probes, polymerase chain reaction (PCR), DNA sequencing, gene chip technology, and the Xpert MTB/RIF test. Although most techniques are highly sensitive and rapid, their application and dissemination in most high TB-burden countries have been severely limited by the high prices and specialized instrument requirements. In the 1920s, it was discovered that lytic bacteriophages had the capacity to eradicate bacteria with a high degree of specificity. Phage therapy was developed and is currently used in a number of Eastern European nations, including Georgia, Russia, and Poland . Bacteriophages were discovered in the early 20th century in 1915 by Frederick Twort and in 1917 by Felix d'Herelle, working independently . [5]He began actively using them as preventive and therapeutic agents against bacterial infections, primarily medicating patients who suffered from intestinal bacterial diseases such as dysentery and cholera. This practice continued until the discovery of antibiotics . Phage research and medicinal applications were most fruitful in the second and third decades of the 20th century. However, the focus on bacteriophage therapies slumped with the development of antibiotics after World War II . Between 2020 and 2021, there was a 3.1% increase in drug-resistant TB, accounting for 450 000 cases. The creation of novel treatment plans has been hampered by the lack of understanding regarding the membrane structure of antibiotic-resistant Mtb strains, as well as the mechanisms by which these bacteria acclimate to different site organs, such as the lung . The widespread rise in mycobacterial strains that are resistant to drugs highlights the urgent need for alternatives to antibiotics. Mycobacteriophages are becoming increasingly common as a treatment option for TB. The effectiveness of mycobacteriophages against both widespread and multidrug-resistant TB has been assessed. In animal studies, there was some success in preventing the spread of TB in guinea pigs. However, phage-mediated direct regulation of TB may not be a viable therapeutic option because TB microorganisms can create granulomas. Below, we introduce the major strategies for bacteriophage therapy currently in use, which include engineered bacteriophages, bacteriophage cocktails, bacteriophage delivery, and bacteriophage and antibiotic combinations, citing recent studies of each strategy in Mycobacterium spp. Finally, we describe the advantages, limitations, and immune system response to bacteriophage therapy.[7]

In the bioengineering field, innovative vaccine systems can be created by using bacteriophages. Designer DNA phage vaccines have the advantage of being able to both treat and prevent infection. Additionally, large populations could be immunized with bacteriophage vaccines, which feature low production costs and ease of use. In 2004, Jepson and March proposed the idea of providing bacteriophage DNA vaccinations orally through drinking water. Notably, a high phage titer would be necessary for the proposed immunization regimen because phage penetration and gut transit following oral delivery are apparently dose-dependent. In addition, by using genetic bioengineering techniques, the potential for phage gene toxicity to humans that has been cautioned by some study authors could be removed. To avoid these types of problems, the functions of the phage genes and proteins should be determined prior to using them in clinical studies.In conclusion, genetic engineering not only addresses the issue of phage resistance, but also has the potential to suppress the immune response to therapeutic phages. [9] Phages used in conjunction with antibiotics—referred to as phage antibiotic combination or phage antibiotic synergy—offer the potential for additive, antagonistic, or synergistic effects. There are several strategies behind such combination, which include using phages to increase antibiotic action and administering antibiotics to stop the emergence of bacteria resistant to phages. These methods may involve giving antibiotics and phages either in a sequential or contemporaneous manner. It has been shown that a reduction in bacterial populations achieved through phage-antibiotic synergy, using antibiotics at doses lower than the minimum inhibitory concentration, can stimulate phage output. A small peptide produced by mycobacteriophages, AK15, and an engineered isomer,

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AK15-6, have both been shown to have potent anti-Mtb properties. By disrupting the membrane, AK15 and AK15-6 directly inhibit Mtb. Together with rifampicin, they demonstrated cell selectivity and synergistic effects, successfully reducing the number of Mycobacteria in the lungs of infected Mtb mice. A study using rifampicin combined with a five-phage cocktail (D29, TM4, Che7, PDRPv, and PDRPxv) observed a prominent decrease in bacterial growth, while a study of synergy between different anti-bacterial drugs and phage Muddy found that rifabutin (RFB) had good effectiveness. These authors demonstrated that GD01-infected CF transmembrane conductance regulator-depleted zebrafish could be cured via treatment with RFB, Muddy, or an RFB and Muddy combination. They concluded that the therapeutic synergy between Muddy and RFB strongly increased the survival rate compared with that in larvae treated with either RFB or Muddy alone, reaching 70% survival at 12 days post-infection, which was approximately the same as that for GD01 infection in wild-type zebrafish. Beyond the above-mentioned strategies, other techniques involving bacteriophages are being used to treat infections. For example, phage display technology is an effective method for locating small peptides that have the ability to target and bind molecules, thereby controlling their function. [8] The foundation of this technique is the connection between phage genotype and surface phenotype. Nanotechnology is another recent technological advancement in biomedicine, with applications that span disease diagnosis to medication delivery.

In summary, phage therapy has become a backup option for treating infections caused by resistant bacteria. One commonly used strategy entails combining phages with antibiotics; however, it is worth investigating whether some antibiotics have antagonistic effects on phages.

Mycobacteriophages, a type of bacteriophage specific to mycobacteria, have shown promise as an alternative to traditional antibiotics, particularly in the fight against tuberculosis (TB). These viruses have the unique ability to infect and lyse specific pathogenic bacteria, offering a targeted approach that spares the beneficial microbiota often disrupted by broad-spectrum antibiotics. Their specificity also lends to the precise diagnosis of TB, as they can detect and indicate the presence of mycobacterial infections. Studies have demonstrated the potential of mycobacteriophages in both the diagnosis and treatment of TB, with clinical applications being explored for their use in phage therapy, especially in regions where antibiotic resistance is prevalent. Furthermore, research indicates that mycobacteriophages may work synergistically with antibiotics, enhancing the efficacy of drug treatments against resistant strains of mycobacteria. The exploration of mycobacteriophages as therapeutic agents opens up new avenues in the management of mycobacterial infections, potentially revolutionizing the approach to combating antibiotic-resistant bacteria.

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