OPEN ACCESS Freely available online

Mycobacterial Diseases

ISSN: 2161-1068

Opinion Article

Phage Impact on *Mycobacterium abscessus* Lung Disease

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DESCRIPTION

Mycobacterium abscessus is a rapidly growing Nontuberculous Mycobacterium (NTM) that poses significant challenges in clinical treatment due to its intrinsic resistance to many antibiotics. Particularly problematic in Cystic Fibrosis (CF) and immunocompromised patients, *M. abscessus* lung infections are notoriously difficult to eradicate. As traditional antibiotic therapies fall short, bacteriophage (phage) therapy, which employs viruses that specifically infect and kill bacteria, has emerged as a promising alternative. This article explores the host and pathogen responses to engineered bacteriophages targeting *M. abscessus* in lung infections.

Pathogen response to bacteriophage therapy

Engineered bacteriophages are designed to recognize and bind specific receptors on the surface of *M. abscessus*. Upon adsorption, phages inject their genetic material into the bacterial cell, initiating the infection process. The effectiveness of this step is important; phages must overcome any bacterial surface modifications or receptor mutations that could impede binding. Once inside, phages hijack the bacterial machinery to replicate their DNA and produce progeny phages. This lytic cycle culminates in the lysis of the bacterial cell, releasing new phages to infect surrounding bacteria. The rapid replication and release of phages can lead to a dramatic reduction in the bacterial population. Bacterial resistance to phages can develop through various mechanisms, including receptor modification, CRISPR-Cas systems, and restriction-modification systems. Understanding these mechanisms is vital for engineering phages that can evade or overcome bacterial defenses, ensuring sustained efficacy of the therapy.

Host response to bacteriophage therapy

Innate immune response: The host's innate immune system is the first line of defense against infections. The lysis of bacteria by phages releases bacterial components such as lipids and proteins, which can trigger an inflammatory response. This response is characterized by the recruitment of immune cells like macrophages and neutrophils to the site of infection, enhancing bacterial clearance. Phage therapy can influence the production of cytokines, signaling molecules that orchestrate the immune response. For instance, phage-induced bacterial lysis can lead to increased levels of pro-inflammatory cytokines, aiding in the fight against infection but also posing a risk of excessive inflammation.

Adaptive immune response: Phages can interact with the adaptive immune system, though this interaction is less understood than the innate response. The immune system may produce antibodies against phages, potentially neutralizing their therapeutic effects. Strategies such as using a cocktail of different phages or engineering phages to evade the immune system are employed to mitigate this response. Repeated exposure to phages can lead to immune memory, potentially affecting the long-term efficacy of phage therapy. Understanding this aspect is important for developing phage therapies that remain effective over prolonged treatment periods.

Microbiome impact: Phage therapy can also affect the host's microbiome. While targeting pathogenic *M. abscessus*, phages may inadvertently impact commensal bacteria, leading to dysbiosis. However, the specificity of phages generally results in a more targeted approach than broad-spectrum antibiotics, potentially preserving the overall microbiome balance.

Clinical implications

Clinical studies have demonstrated the potential of engineered phages in treating *M. abscessus* lung infections, particularly in patients with CF. Phage therapy offers a viable alternative where antibiotic treatments have failed, showcasing impressive bactericidal activity and improved clinical outcomes. Despite its promise, phage therapy faces challenges such as the development of bacterial resistance, immune system interactions, and regulatory hurdles. Future research should focus on optimizing phage design, understanding host-pathogen interactions, and conducting large-scale clinical trials to establish safety and efficacy standards.

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Received: 03-Apr-2024, Manuscript No. MDTL-24-32626; **Editor assigned:** 05-Apr-2024, PreQC No. MDTL-24-32626 (PQ); **Reviewed:** 19-Apr-2024, QC No. MDTL-24-32626; **Revised:** 26-Apr-2024, Manuscript No. MDTL-24-32626 (R); **Published:** 03-May-2024, DOI: 10.35248/2161-1068.24.14.459.

Citation: Rebecca J (2024) Phage Impact on *Mycobacterium abscessus* Lung Disease. Mycobact Dis. 14:459.

CONCLUSION

Bacteriophage therapy represents a novel and promising approach to combating *M. abscessus* lung infections. By leveraging the natural predator-prey relationship between phages and bacteria, this therapy offers targeted, efficient bacterial eradication. Continued research and clinical validation are essential to fully realize its potential and integrate it into standard treatment protocols for refractory mycobacterial infections.