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Host-Directed and Macrophage-Targeted Nanoparticle Systems in Pulmonary Tuberculosis Therapy: Mechanistic Insights and Therapeutic Advances

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Abstract
Pulmonary tuberculosis (TB), caused by Mycobacterium tuberculosis, remains a major global health challenge due to prolonged treatment duration, poor patient compliance, and emergence of multidrug-resistant strains [1,2]. Conventional anti-tubercular therapy is often limited by non-specific drug distribution, systemic toxicity, and inadequate intracellular drug delivery [3,4]. In recent years, host-directed therapy (HDT) has emerged as a promising approach aimed at modulating the host immune response to improve treatment outcomes [2,5]. Simultaneously, nanoparticle-based drug delivery systems have demonstrated significant potential in enhancing drug targeting and bioavailability [6,7]. The integration of HDT with macrophage-targeted nanoparticle systems offers a dual therapeutic strategy by combining antimicrobial activity with immune modulation [3,8]. These systems facilitate targeted drug delivery to infected macrophages, enhance intracellular drug concentration, and activate immune pathways such as autophagy for improved bacterial clearance [5,9]. This review provides a comprehensive overview of TB pathophysiology, limitations of conventional therapy, and recent advances in host-directed and nanoparticle-based approaches. Special emphasis is placed on macrophage targeting strategies, drug–immune synergy, and future perspectives including smart nanocarriers and personalized medicine.

Keywords: Pulmonary tuberculosis; Host-directed therapy; Macrophage-targeted nanoparticles; Nanomedicine; Rifampicin delivery; Immune modulation; Autophagy; Pulmonary drug delivery.

1. Introduction

Tuberculosis continues to be one of the leading causes of mortality worldwide, particularly in developing countries [10]. According to the World Health Organization, millions of new TB cases are reported annually, with a significant proportion associated with drug-resistant forms such as MDR-TB and XDR-TB [10]. The standard TB treatment regimen involves a combination of drugs administered over a prolonged period of 6–9 months, which often leads to poor patient adherence and treatment failure [11].
Conventional anti-tubercular drugs, including Rifampicin, are effective but suffer from several limitations such as low bioavailability, systemic toxicity, and inability to efficiently penetrate intracellular

compartments where the pathogen resides [12,13]. Since TB bacteria primarily survive within macrophages, effective treatment requires targeted delivery of drugs to these cells [3].
Nanotechnology-based drug delivery systems have gained considerable attention due to their ability to improve drug solubility, stability, and targeted delivery [14,15]. Additionally, host-directed therapy focuses on enhancing the host immune response to combat infection [2,5]. The combination of these two approaches represents a promising strategy for improving TB treatment outcomes [6,8].

2. Pathophysiology of Tuberculosis

Tuberculosis infection begins when aerosolized droplets containing Mycobacterium tuberculosis are inhaled and deposited in the alveolar region of the lungs [10]. The bacteria are engulfed by alveolar macrophages, which serve as the primary host cells. However, instead of being destroyed, the bacteria have evolved mechanisms to survive and replicate within macrophages [16].
One of the key features of TB infection is the formation of granulomas, which are organized structures composed of immune cells that attempt to contain the infection [17]. Within these granulomas, the bacteria can remain dormant for extended periods.
The intracellular survival of TB bacteria is facilitated by their ability to inhibit phagosome-lysosome fusion, thereby escaping degradation [18]. This highlights the importance of developing therapeutic strategies that enhance intracellular drug delivery and immune-mediated bacterial clearance.

3. Host-Directed Therapy (HDT)

Host-directed therapy represents a novel approach that focuses on modulating the host immune response rather than directly targeting the pathogen [2,5]. HDT aims to enhance the ability of the host immune system to eliminate the infection while reducing inflammation and tissue damage.

Key mechanisms involved in HDT include:

Activation of autophagy pathways
Modulation of cytokine production
Enhancement of macrophage bactericidal activity [5,19]

Agents such as metformin, vitamin D, and rapamycin have been shown to promote autophagy and improve TB outcomes [5]. HDT also plays a crucial role in reducing drug resistance by minimizing the reliance on antibiotics alone [2].

4. Nanoparticles in Tuberculosis Therapy

Nanoparticles offer several advantages in drug delivery, including improved bioavailability, controlled release, and targeted delivery [20,21].
Various types of nanoparticles have been explored for TB therapy:
Polymeric nanoparticles (e.g., PLGA)
Liposomes
Solid lipid nanoparticles
Nanoemulsions [22,23]
These systems enhance drug stability and enable sustained release, thereby reducing dosing frequency [24]. Importantly, nanoparticles can be engineered to target specific cells, such as macrophages, which are the primary site of TB infection [3].

5. Macrophage Targeting Mechanism

Macrophage targeting is a critical aspect of nanoparticle-based TB therapy [3]. Targeting can be achieved through surface functionalization of nanoparticles with ligands that bind to receptors on macrophages [7].

Common targeting ligands include:

Mannose (targets mannose receptors)

Folic acid (targets folate receptors)

Antibodies [9]

These ligand-functionalized nanoparticles are internalized by macrophages through receptor-mediated endocytosis, leading to enhanced intracellular drug delivery [7]. This targeted approach significantly improves therapeutic efficacy while reducing systemic toxicity [25].

6. Drug + Immune Modulation Synergy

The combination of antimicrobial drugs and immune modulators represents a synergistic approach for TB treatment [2,5]. For example, rifampicin-loaded nanoparticles can be combined with autophagy activators such as metformin [5].

In this strategy:

Rifampicin provides direct bactericidal activity

Autophagy activators enhance intracellular bacterial clearance

This dual mechanism leads to improved treatment outcomes, reduced drug resistance, and enhanced therapeutic efficiency [6,8].

7. Advantages

The integration of host-directed therapy with nanoparticle-based drug delivery offers several advantages [3,6]:

Targeted delivery to infected macrophages

Enhanced intracellular drug concentration

Reduced systemic toxicity

Improved patient compliance

Lower risk of drug resistance

8. Challenges

Despite the promising potential, several challenges remain [20,21]:

Scale-up and manufacturing difficulties

Stability of nanoparticle formulations

Regulatory and safety concerns

Limited clinical data

Addressing these challenges is essential for the successful translation of these systems into clinical practice.

9. Future Perspectives

Future research should focus on the development of smart and stimuli-responsive nanoparticles that can release drugs in response to specific triggers such as pH or enzymes [4]. Integration of artificial intelligence for nanoparticle design and personalized medicine approaches may further enhance treatment

outcomes.
Additionally, the development of inhalable nanoparticle systems for pulmonary delivery represents a promising direction for targeted TB therapy [15].

10. Conclusion

Host-directed and macrophage-targeted nanoparticle systems represent a promising advancement in TB therapy [3,6]. By combining antimicrobial activity with immune modulation, these systems offer a comprehensive approach to overcoming the limitations of conventional therapy. Continued research and clinical validation are essential to fully realize their potential in improving global TB treatment [2,10].

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