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Antimicrobial peptides in Tuberculosis: Insights into the Immunomodulatory mechanisms

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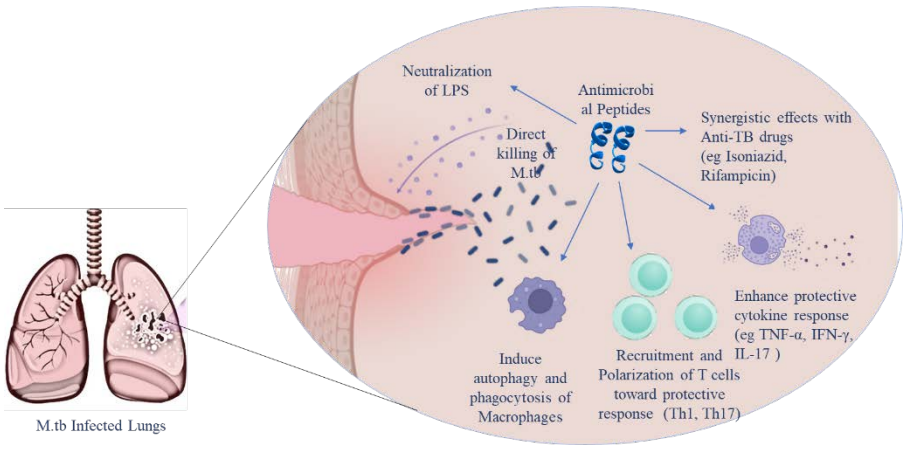
Review

ABSTRACT

Tuberculosis is a highly contagious airborne disease that remains one of the leading causes of mortality worldwide. In the era of an increasing rate of drug-resistant strains and other shortcomings of current anti-TB therapies, we promptly need new, effective treatments to combat tuberculosis. Antimicrobial peptides have emerged as promising candidates, offering a novel approach to tackling tuberculosis, particularly drug-resistant strains. Antimicrobial peptides have broad-spectrum antimicrobial activity and the ability to modulate host immune responses. Their unique mechanism of disrupting microbial membranes reduces the likelihood of resistance development. Additionally, antimicrobial peptides can enhance immune function by recruiting immune cells, promoting phagocytosis and modulating innate and adaptive immune responses. These properties make antimicrobial peptides particularly effective in managing infections like tuberculosis while the generation of drug-resistant and excessive inflammation, a critical consideration in tuberculosis treatment.



Keywords: Mycobacterium tuberculosis, antimicrobial peptides, Anti-TB therapy, immunomodulation, anti-mycobacterial compounds, MDR/XDR TB, T cells, cytokines.

INTRODUCTION

In 1882, Robert Koch discovered *Mycobacterium tuberculosis* (M.tb), the cause of Tuberculosis (TB), which marked an important milestone in the medical profession.[1] However, despite this key finding, TB persists as a global health problem that affects millions of people every year.[2] M.tb affects the respiratory system mainly leading to pulmonary TB, but it can also transmit to other parts of the body resulting in extrapulmonary TB.[3] Some infected individuals remain asymptomatic for years and still harbour the bacteria in a dormant stage. This dormant M.tb leads to a condition known as Latent Tuberculosis (LTBI).[4] When these individuals encounter an immunocompromised condition, bacilli become active and cause active TB. The COVID-19 pandemic has slowed down the progress made till 2020 in reducing TB incidences.[2] According to WHO, almost 10.6 million people were globally diagnosed with tuberculosis in 2022 which was more than the past two years. The incidence rate of TB is reported to increase by 1.9% per 100,000 people annually during 2020 and 2022.[2] India accounts for 27% of the global tuberculosis burden, positioning it as the country with the largest share of TB cases worldwide.[2] Latent TB patients have a lifetime risk of having tuberculosis. The risk of developing active TB is 18 times higher in patients suffering from HIV.[6] To combat TB effectively, sustained monitoring, strong prevention measures and advanced therapeutic strategies are essential. The intensive global efforts in these areas remain decisive in the relentless struggle against this persistent pathogen. The Global TB Report 2023 highlights the urgent need for the development of new targeted interventions, along with robust public health strategies, to achieve the ultimate goal of eradicating tuberculosis.[2]

PATHOGENESIS

The development of TB disease is driven by a complex interaction between the M.tb and the host's immune system. Crucial factors contributing to disease progression include the bacteria's strong resistance, virulence and ability to thrive as a

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parasite, as well as host-related factors like age, nutritional status and immune health.[5] TB is transmitted from one individual to another via airborne particles. When an individual suffering from infectious TB (transmissible TB) coughs or sneezes, minute particles containing M.tb may be expelled into the atmosphere.[6] These M.tb-containing droplet nuclei can remain airborne for minutes to hours after expectoration. Once inhaled, these infectious droplets settle throughout the airways. Most of the bacilli are trapped in the upper parts of the airways where the mucus-secreting goblet cells exist.[6] This system offers the body a primary line of physical defense that helps to avert infection in the majority of individuals who come into contact with tuberculosis.[7] If bacilli in droplets bypass the mucociliary system and reach the alveoli, bacilli will be quickly surrounded and engulfed by alveolar macrophages. After being ingested by macrophages the mycobacteria continue to multiply, whereas macrophages produce proteolytic enzymes and cytokines in an attempt to degrade the bacteria.[7] The Antigen-presenting cells lead T lymphocytes to the lungs, the cells that constitute cell-mediated immunity. Further activation of other immune cells such as dendritic cells, monocytes, neutrophils and T cells causes the aggregation of immune cells and granuloma formation in the lungs.[5] M.tb proliferates until it achieves a critical mass that effectively triggers the cell-mediated immune response, resulting in delayed hypersensitivity. Which can be detected by the tuberculin (Mantoux) test.[8,9] Granuloma is a central caseation necrosis. Sometimes granulomas can become abscesses that lead to cavitation a lesion seen in the lung which can be detected in chest X-ray.[10] The lesions consist of a calcified focus of the infection and an associated lymph node to control active TB infection. In other words, the bacilli have four potential fates inside the host body: first, bacteria will be killed and cleared by the immune system, second M.tb will survive, multiply and cause primary TB. The Third bacilli may become dormant and remain asymptomatic (latent TB) for years and the fourth M.tb proliferates after a latency period causing disease reactivation.[10] Individuals with latent TB cannot transmit tuberculosis to others. These individuals pass through fibrosis and calcification, successfully controlling the infection.[6] M.tb can remain dormant in necrotic tissue for extended periods and if an individual's immune system becomes compromised later on, there is a potential for the disease to reactivate.[11] Inside the granuloma, M.tb continues to multiply. When the mycobacteria reach a critical mass, the granuloma is unable to contain the infection, leading to the dissemination of M.tb to other organs, such as the brain.[12] At this point, the pathogen may enter the bloodstream or re-enter the respiratory tract, making the host symptomatic and contagious, which is known as active TB disease.[12] Immunity to M.tb involves an interplay between the innate and adaptive immune response. During early infection, alveolar macrophages are a major source of proinflammatory cytokines (TNFα, IFN-γ), although stromal cells can generate cytokines and chemokines, which can influence immune responses as well.[11] During this period, dendritic cells travel from the lungs to the lymph node via CCR7 and prime naive T cells to initiate adaptive immune responses. The replicating pathogen triggers a rapid and intense response, leading to the recruitment of both neutrophils and monocytes from the bone marrow through the induction of proinflammatory cytokines and chemokines.[13] Coordinated cytokine and chemokine induction is crucial for the regulation of cellular recruitment.[14,15] While initial recruitment of monocytes requires type I IFN, overexpression of this cytokine leads to high levels of CCR2-expressing monocytes which have limited potential to control M.tb growth.[16] IL-17 promotes the secretion of Type II IFN such as IFN-γ regulates the recruitment of neutrophils in the lungs.[16] Further, dendritic cells and macrophages migrate to the draining lymph node using both cytokine (IL-12p40) and chemokine (CCR2, CCR7) pathways.[17] Antigen-presenting cells (APCs) stimulate naïve T cells via MHC class I and class II, releasing cytokines and chemokines that enhance T-cell proliferation and polarization. Activated T cells migrate through the vasculature to the inflamed site.[18,19] Some T cells remain in the vasculature ($CX3CR3^{+}$), while others move into the parenchyma ($CXCR3^{+}CCR6^{+}$). The expression of CXCR5 on antigen-specific T cells enables them to respond to IL-23- and IL-17-dependent CXCL13, facilitating their effective localization within the granuloma, where they activate M.tb-infected macrophages.[13] In the lungs, T cells release various cytokines, including IFN-γ, TNFα, IL-17and IL-10, which can have both protective and detrimental effects depending on the context.[18] Although a proinflammatory response is beneficial for eliminating infections, it may also lead to excessive inflammation and subsequent tissue damage.[16] There is a continuous tug-of-war between proinflammatory cytokines, anti-inflammatory cytokines and regulatory T cells, which ultimately determines the infection's outcome.

Challenges to the Standard Treatment

The currently available tuberculosis treatment, known as anti-tuberculosis therapy (ATT), is effective for drug-sensitive strains but is lengthy and has significant drawbacks. These therapeutic agents are toxic and contribute to the emergence of various drug-resistant strains of M.tb. Additionally, Isoniazid, a first-line anti-tb drug is reported to weaken immune responses, making the host more vulnerable to disease reactivation and reinfection, suggesting that ATT may impair the immune system.[20] Prolonged exposure to anti-TB drugs causes gut microbiota imbalance, reducing its functional potency and potentially leading to poor treatment outcomes.[21] ATT increases disease relapse rate by dampening innate and adaptive immune responses by impairing key signaling pathways like STAT3, STAT4, FOXO1and NFκB, leading to reduced T cell memory.[22] This underscores the need for integrating immunomodulatory agents to enhance treatment efficacy. The rise of drug-resistant strains of M.tb, including multidrug-resistant (MDR) and extensively drug-resistant (XDR), poses significant challenges.[23] M.tb has developed resistance to all drugs used against it, including recently introduced ones.[24] Unfortunately, current treatment protocols for TB have not evolved to address the growing issue of drug resistance, rendering them insufficient for effectively managing drug-resistant TB. [25] (Figure 1)

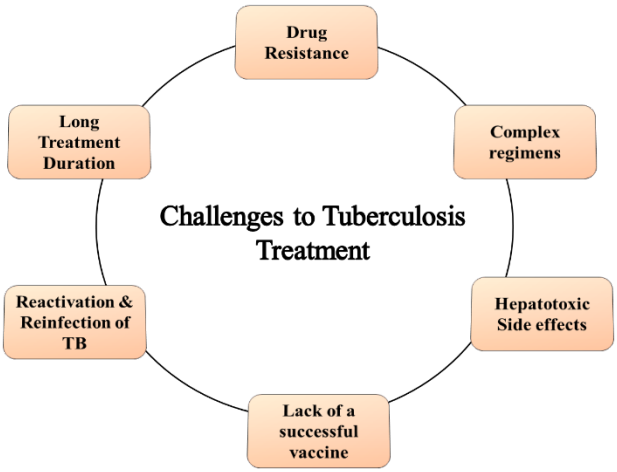

Figure 1. Challenges to current TB Treatment.

Another challenge in the eradication of TB is no effective vaccine is available to prevent TB in adults.[26] However, the licensed TB vaccine, Bacille Calmette-Guérin (BCG), developed nearly a century ago, does offer moderate protection for infants and children, particularly against severe TB forms like miliary TB and TB meningitis.[27] Whereas TB can affect anyone, approximately 90% of active TB cases occur in adults, with a higher incidence among men than women.[28,29] As an obligate human pathogen with a highly conserved genome, M.tb has adapted to its niche over thousands of years, allowing for the detailed reconstruction and dating of its phylogenies.[30] This helps us understand how resistance is acquired and spread globally. Resistance to new drugs typically occurs within five to ten years of clinical use and is even more rapid for the latest drugs.[31] Resistance to new drugs like bedaquiline and delamanid is caused by rare mutations across large genomic targets. These mutations have been detected quickly, making it difficult to statistically correlate genotype and phenotype.[32] Therefore, it is essential to develop innovative strategies for detecting mutations that confer resistance to new medications before the establishment of widespread resistance, which could diminish their efficacy.[33] Consequently, there's an urgent need for a more effective vaccine that provides immunity across all age groups and targets all TB forms.[27]Additionally, we require new anti-TB drugs that surpass current treatment options in terms of efficacy, tolerance and treatment duration to combat TB's spread. As a result, urgent efforts are needed to develop novel anti-TB drugs that can effectively combat drug-resistant bacteria and eliminate persistent infections.

Antimicrobial Peptides: A New Strategy to Combat Tuberculosis

The high prevalence rate of drug-resistant strains and the limitations of current ATT underscore the immediate requirement for new, effective treatments. Antimicrobial peptides (AMPs) stand out as a promising class of therapeutic agents, especially in the era of rising drug resistance.[34] AMPs, with their distinctive properties like short sequences (typically 20–60 amino acids), cationic charge and amphipathic structure are uniquely equipped to meet this challenge.[35] Their ability to interact with both aqueous environments and lipid-rich microbial membranes allows AMPs to bind and disrupt the negatively charged membranes of bacteria, leading to cell death.[36,37] This membrane-targeting mechanism contributes to their broad-spectrum activity against Gram-positive and Gram-negative bacteria, fungi, viruses and even parasites and reduces the likelihood of pathogens developing resistance.[38] This is a crucial advantage in the ongoing battle against antibiotic-resistant infections. Furthermore, AMPs can be classified into several structural categories, such as α-helices, β-hairpins, antiparallel β-sheets and linear peptides. Each of these structures contributes to their function, by disrupting microbial membranes directly or translocating across the membrane to target intracellular components.[35] The versatility in their modes of action makes AMPs adaptable to various therapeutic contexts, whether as stand-alone treatments or in synergy with existing drugs.[39] The advent of new methodologies in peptide synthesis and delivery has further expanded the potential of AMPs in clinical settings.[40] These advances may lead to the development of AMP-based therapies that are not only effective against a broad range of pathogens but also safe and economically viable.[41] AMPs represent a vital and versatile tool in modern medicine, offering new hope in the fight against increasingly resistant infections and setting the stage for innovative treatments that could reshape our approach to infectious diseases such as TB management.[42] (Figure 2).

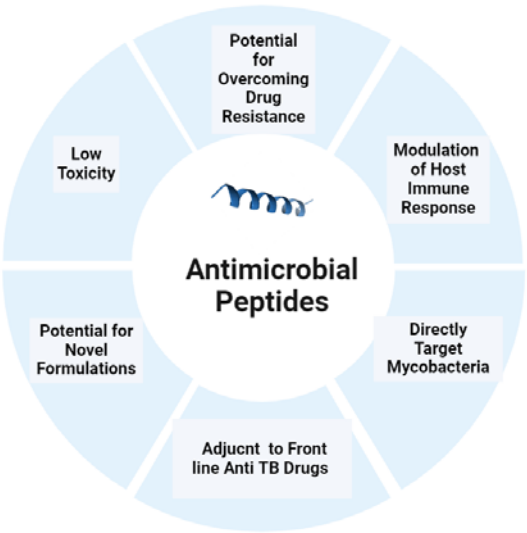

Figure 2. Properties of antimicrobial peptides to combat TB.

AMPs have a dual function in host defense: they can directly kill pathogens and modulate the immune system, affecting both innate and adaptive immune responses.[43] *In vitro* and *in vivo* studies have shown that AMPs exhibit direct antibacterial activity against intracellular bacteria, including *Mycobacterium tuberculosis*, as well as other pathogens like *Nocardia spp.*, *Listeria monocytogenes*and drug-resistant *Salmonella enterica*.[44] AMPs can target these bacteria effectively, though they are less frequently reported.[45] AMPs stand out due to their ability to both modulate the host's immune response and directly kill microbes,

making them ideal for managing infections while preventing excessive inflammation.[46] Immunomodulation is particularly advantageous in treating infectious diseases such as TB, as it enhances the immune system and regulates inflammation without directly targeting the pathogen, making it especially useful for combating antibiotic-resistant or intracellular bacteria (M.tb) that are difficult to eliminate.[46] AMPs can enhance or suppress immune responses depending on various factors, such as environmental conditions and specific cells and receptors involved.[44] In innate immunity, AMPs like defensins and cathelicidin play roles beyond pathogen destruction, including recruiting immune cells like neutrophils, eosinophilsand macrophages to infection sites.[47,48] They can also enhance phagocytosis, stimulate the production of chemokines and cytokinesand influence neutrophil lifespan and function.[49,50] Certain AMPs play a role in regulating inflammation, either enhancing or inhibiting inflammatory responses based on the specific circumstances. In adaptive immunity, AMP link innate and adaptive responses by attracting antigen-presenting cells, such as dendritic cells (DCs), to infection sites.[51] They also promote DC maturation, leading to enhanced T cell activation and polarization towards Th1 responses, which are crucial for effective immune defense.[51] Additionally, AMPs can modulate humoral responses by acting as adjuvants to increase specific antibody production while influencing cytokine production by B cells.[52] The primary role of AMPs in infection resolution appears to be through immune modulation rather than direct pathogen killing. As illustrated in Figure 3, the experimental design is structured to evaluate the immunomodulatory effects of AMPs against M.tb.

Their immunomodulatory effects, including enhancing phagocytosis, promoting DC maturation and regulating cytokine production, play a significant role in overcoming infections like TB.[53] Evidence indicates that even AMPs with limited direct antimicrobial activity can significantly decrease bacterial burdens and inflammation *in vivo* by influencing the immune system.[53] In this Review, we focus on the immunomodulatory potential of AMPs in TB (Table 1) and discuss how these peptides influence host immune responses to enhance pathogen clearance (Figure 4). The detailed discussion will elucidate the mechanisms by which AMPs modulate both innate and adaptive immunity in the context of tuberculosis.

IMMUNOMODULATORY ANTIMICROBIAL PEPTIDES

Lactoferrin

Lactoferrin is an 80 -kDa iron-binding glycoprotein found in various mammalian secretions like saliva, tears and milk, with an iron-binding affinity 300 times higher than serum transferrin.[54] It plays a significant role in the innate immune system because of its antimicrobial and immunomodulatory properties, particularly in oral defense.[54,55] Proteases acting on Lactoferrin produce peptides with antimicrobial activity, such as hLF (1-11), which is undergoing clinical trials for treating infections like *Klebsiella pneumoniae*, *Listeria monocytogenes* and methicillin-resistant *Staphylococcus aureus* (MRSA).[56,57] Another Lactoferrin-derived peptide, LFcin17-30, has shown significant immunomodulatory activity against *Mycobacterium avium*, although its effectiveness against M.tb has not been reported.[58,59] Although a direct killing effect of Lactoferrin on M.tb has not been reported, its immunomodulatory action indirectly kills the bacilli. Lactoferrin demonstrates a strong interaction with membranes and has been proven to influence the immune system in its fight against M.tb. In a mouse model, oral Lactoferrin treatment reduced bacterial spread to the liver, lowered lung bacterial counts and increased proinflammatory mediators like IL-12.[60] Additionally, Lactoferrin enhances the IL-12/IL-10 ratio, promoting a Th1 response, which provides protection against M.tb.[61] Moreover, Lactoferrin improved the efficacy of

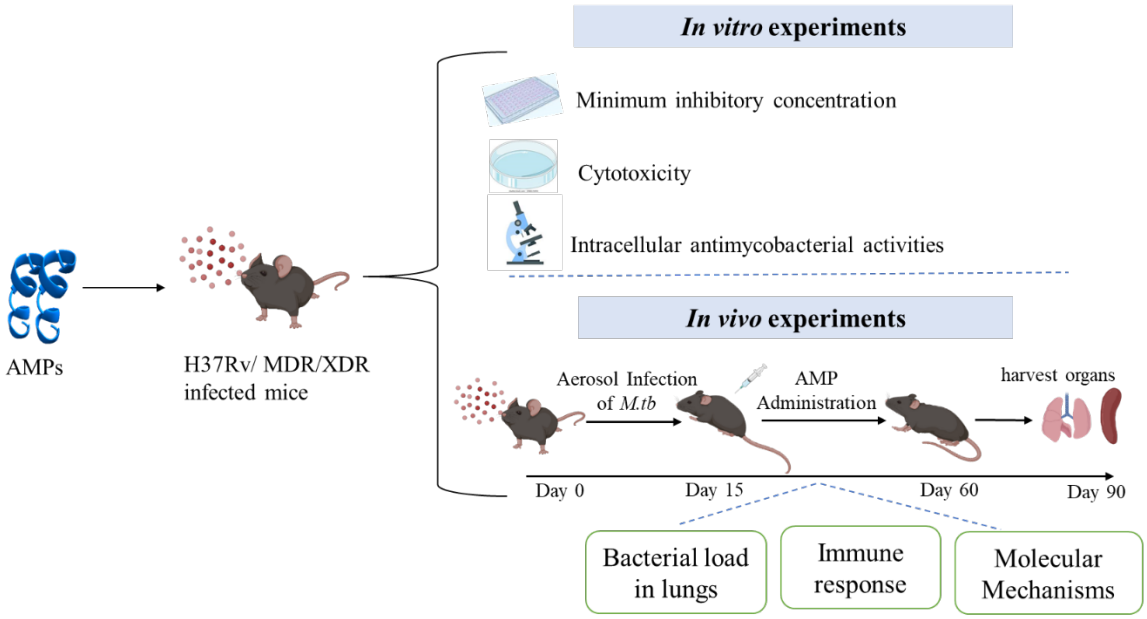

Figure 3: The experimental design to evaluate the Immunomodulatory effect of AMPs against M.tb.

the BCG vaccine when used as an adjuvant, reinforcing its anti-tubercular potential.[62,63] The control M.tb infection depends on cellular immunity, particularly a strong T-cell helper 1 (Th1) response. Researchers explored the use of Lactoferrin, as an adjuvant to enhance the efficacy of the BCG vaccine against TB.[64] Lactoferrin was initially found to increase IL-12(p40) production in macrophages stimulated with LPS, a crucial step for initiating a Th1 response.[65,66] In studies with mice, a single immunization with Lactoferrin as an adjuvant led to a stronger splenocyte proliferative response to heat-killed BCG and elevated IL-12(p40) levels, with an increased IL-12/IL-10 ratio. The immune response was further enhanced, as evidenced by the increased production of proinflammatory mediators such as TNF-alpha, IL-1betaand IL-6, nearing the levels seen with the potent adjuvant complete Freund's adjuvant (CFA). Notably, IFN-γ production during antigenic recall was significantly elevated, a key indicator of a strong Th1 response.[66,67] When mice immunized with the Lactoferrin-adjuvanted BCG vaccine were later exposed to virulent M.tb via aerosol challenge, they showed reduced bacterial loads in the lungs and limited spread of the infection to other organs, such as the spleen. These findings suggest that Lactoferrin can effectively enhance cellular immunity and boost the protective efficacy of the BCG vaccine against TB.[64,67] However, M.tb can acquire iron from Lactoferrin through GAPDH, which also binds transferrin.[68] Lactoferrin also alters bacterial membrane permeability by interacting with negatively charged LPS and it shows synergistic effects against gram-negative bacteria with first-line anti-TB drugs rifampin.[69] It has been shown to enhance IL-17 production, which reduces M.tb burden in the lungs.[69] Lactoferrin-treated mice showed reduced lung inflammation, increased $CD4^+$ and $CD8^+$ cells and enhanced IFN-γ and IL-17-producing cells, which provide protection against M.tb infection.[70] Although Lactoferrin did not directly suppress M.tb growth in either macrophages or broth culture, it enhanced IFN-γ-mediated killing through a nitric oxide-dependent pathway.[70] In summary, Lactoferrin shows potential as a promising therapeutic agent for TB, with the ability to reduce immune-mediated tissue damage and significantly enhance the efficacy of the BCG vaccine. By boosting cellular immunity and promoting a strong Th1 response, Lactoferrin could play a crucial role in improving TB treatment and vaccine outcomes.

Cathelicidins

Cathelicidins are a family of AMPs found in mammals, with around 30 known types. However, in humans, rhesus monkeys, rats, mice and guinea pigs, only one type is expressed: LL-37 in humans, RL-37 in rhesus monkeys, rCRAMP in rats, mCRAMP in mice and CAP11 in guinea pigs. This peptide is produced by various cells, especially neutrophils, in response to infections.[71] In humans, Cathelicidins AMP genes encode the precursor hCAP18, which is then cleaved to form the active LL-37 peptide. Cathelicidins are antimicrobial peptides found in humans and animals, playing a key role in innate immunity by fighting bacteria, viruses and fungi. They not only have direct antimicrobial activity but also regulate host defense responses.[72] In humans, LL-37, the only cathelicidin, has broad antimicrobial properties and modulates immune responses, aiding in wound healing and reducing inflammation.[73] LL-37 can bind to bacterial membranes, disrupting them and it also modulates immune responses, including chemotaxis, macrophage differentiation and neutrophil function.[74] Research shows that cathelicidin, particularly LL-37, can enhance the immune system's ability to control intracellular *Mycobacterium tuberculosis* by promoting mycobacterial killing in macrophages.[75] During TB infection, LL-37 is expressed after the vitamin D receptor is upregulated by mycobacterial lipopeptide interacting with Toll-like receptor (TLR)-2.[76] Oral administration of phenylbutyrate and vitamin D3 has been shown to induce LL-37 production in macrophages and lymphocytes, reducing the intracellular load of M.tb. LL-37 production is also linked to TLR-9 activation with M.tb DNA in alveolar macrophages.[77,78] LL-37 exhibits bactericidal activity against M.tb *in vitro* and modulates immune responses in infected macrophages. Initially, it increases pro-inflammatory cytokines like IL-1β and TNF-α, though TNF-α levels decrease with prolonged exposure. LL-37 also boosts anti-inflammatory cytokines such as IL-10 and TGF-β, indicating its dual role in managing inflammation.[79,80] In vivo studies show that LL-37 and its mouse equivalent, mCRAMP, can reduce M.tb burden in infected mice. Additionally, LL-37 inhibits the binding of lipopolysaccharides (LPS) to macrophages, preventing pro-inflammatory cytokine secretion and has the potential for therapeutic use in TB and other conditions.[81–83] LL-37 is currently being tested in clinical trials for its efficacy in treating tumors.[84] A recent study investigated the antitubercular properties of WBCATH, a cathelicidin derived from water buffalo. In vitro, WBCATH demonstrated microbicidal activity against both drug-sensitive and multidrug-resistant M.tb strains, inducing structural damage to the bacteria and enhancing cytokine production in infected macrophages.[85] Further, WBCATH reduced bacterial load in a murine model of progressive pulmonary TB and exerted a synergistic effect with first-line antibiotics (isoniazid, rifampicin, streptomycin). To further strengthen their finding Computational modelling is done to confirm its impact on the mycobacterial membrane. These findings suggest that WBCATH could be a valuable adjunct to existing TB therapies, potentially improving treatment outcomes and reducing antibiotic duration.[85] In summary, cathelicidins, particularly LL-37, play a crucial role in innate immunity by directly combating M.tb and modulating immune responses. The promising antitubercular properties of WBCATH further highlight the potential for cathelicidin-based therapies to enhance current TB treatments and improve patient outcomes.

Glutoxim (NOV-002)

Glutoxim (NOV-002) is an immunomodulatory peptide used as an anti-infective agent, particularly in Russia as an adjunct to traditional therapies for treating pulmonary and disseminated TB infections.[86] Glutoxim is a tripeptide derivative of oxidized glutathione and works by modulating the immune system.[87] In clinical practice, the incorporation of glutoxim into standard tuberculosis treatment shortened the duration required to eliminate the bacterium, speed up the resolution of pulmonary infiltrates and increased post-infection weight gain.[88] Glutoxim

belongs to a new class of drugs called thiopoietins and is considered an immunorehabilitator. It modulates intracellular thiol metabolism, activates cytokine systems and enhances phagocytosis.[88] Preclinical studies have demonstrated that glutoxim has an immunomodulatory mode of action, suggesting that such peptide-based drugs can be both safe and effective.[89] Glutoxim is in phase III trials in the USA as a chemotherapy adjuvant for non-small-cell lung cancer, showing promise in reducing chemotherapy side effects and modulating immune responses. Its focus shifted from TB treatment due to lower TB rates in the USA.[89] Glutoxim and its derivatives have shown potential in reducing the minimum inhibitory concentration of isoniazid for isoniazid-resistant M.tb strains, with a significant dose-dependent effect. This enhancement in isoniazid efficacy highlights glutoxim's promise as an adjunctive therapy in combatting multidrug-resistant tuberculosis.[90,91] In studies involving MDR TB strains, glutoxim combined with second-line TB drugs (cycloserine + rifabutin, cycloserine + protionamide) significantly decreased the growth of intracellular mycobacteria in murine lung tissue cultures by 3-5 times compared with control groups.[92] Additionally, glutoxim helped maintain the vitality and functional activity of lung tissue cells in these studies.[92] A randomized study involving 42 TB patients showed that glutoxim, when added to traditional treatment regimes, effectively shortened the duration of TB symptoms, accelerated sputum conversion to negative and reduced pulmonary inflammation.[88] The drug was particularly advantageous in patients with severe TB complicated by viral or drug-induced hepatitis.[88] Glutoxim, an immunomodulatory peptide, enhances tuberculosis treatment by reducing isoniazid-resistant M.tb and accelerating recovery, particularly in severe cases. It shows promise as an adjunctive therapy for multidrug-resistant TB and is also being tested as a chemotherapy adjuvant in non-small-cell lung cancer.

Defensins

Defensins are small, cationic peptides with broad-spectrum antimicrobial activity against bacteria, viruses and fungi. These peptides are primarily produced by epithelial cells and neutrophils.[93] They function through multiple mechanisms, including direct disruption of bacterial cell membranes and targeting of bacterial DNA.[93] Additionally, defensins neutralize secreted toxins and play a role in chemotaxis.[94] Mammalian defensins are characterized by a β-sheet structure stabilized by six disulfide-linked cysteines and are categorized into alpha, beta and theta subfamilies. In humans, there are six alpha-defensins (HNP1-4, HD-5and HD-6) and several beta-defensins (HBDs) identified through computational analysis.[95] During M.tb infection, the expression of human beta-defensin 2 (HBD2) is upregulated.[96] L-isoleucine administration in mouse models of tuberculosis increased HBD3 and HBD4 levels, correlated with reduced bacterial load and tissue damage.[97] HBD1 has shown inhibitory effects on both drug-susceptible and MDR M.tb strains and its combination with isoniazid has significantly enhanced this effect.[98] Studies suggest that defensins might enhance the antibacterial activity of macrophages, including against M.tb. For instance, HNP-1, combined with isoniazid or rifampicin, increases bacterial cell membrane permeability, thereby improving drug efficacy.[99] Defensins are also being explored for their immunotherapeutic potential, especially in the context of drug-resistant TB, as they enhance the immune response and recruit essential immune cells.[100,101] Recombinant and synthetic defensin variants, such as human β-defensin 3 (HβD3) derivatives, have shown potent activity against drug-resistant M.tb strains and other pathogens.[102,103] These findings highlight the potential of defensins as therapeutic agents, especially for treating infections resistant to conventional antibiotics. Another study demonstrated that adenoviruses delivering HβD3 significantly reduced bacterial load and lung damage in a murine pulmonary TB model, with enhanced effects when combined with antibiotics, suggesting a promising adjuvant therapy for TB treatment.[104] Defensins are considered valuable in the development of new treatments for TB, particularly against resistant strains. They have shown potential in combination therapies with antibiotics and as part of gene therapy strategies

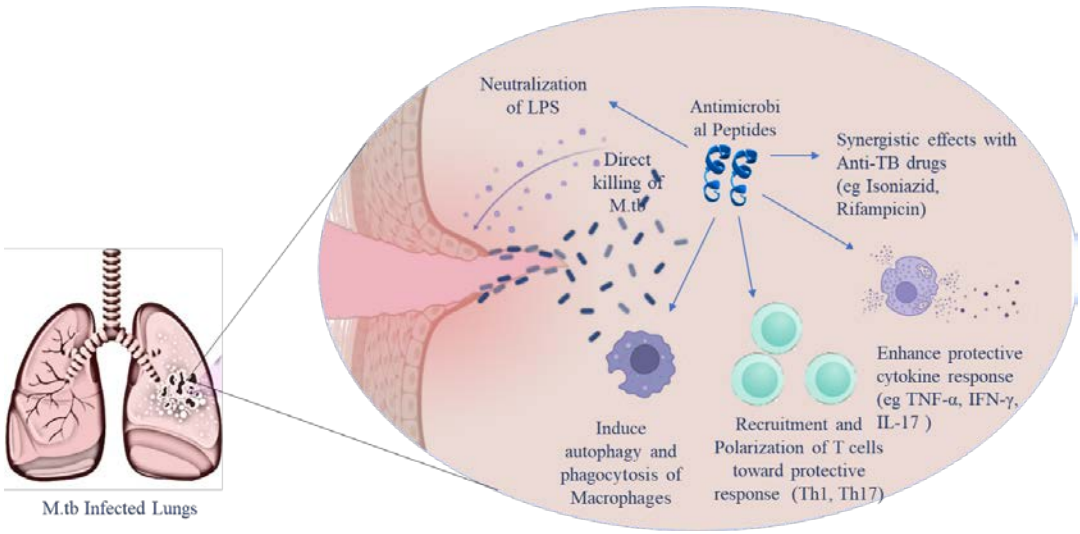

Figure 4: Immunomodulatory mechanisms of antimicrobial peptides against M.tb.

using adenoviral vectors to enhance drug delivery and efficacy.[104] In summary, Defensins, small antimicrobial peptides with broad-spectrum activity, enhance the efficacy of TB treatments, particularly against drug-resistant strains, by disrupting bacterial membranes and boosting immune responses. Studies suggest their potential in combination therapies and as gene therapy agents to improve TB treatment outcomes.

Azurocidin

Azurocidin is a 37-kDa cationic antimicrobial protein located in the azurophilic and secretory granules of polymorphonuclear (PMN) leukocytes, commonly known as neutrophils.[105] Due to its strong affinity for heparin, it is often referred to as heparin-binding protein (HBP).[106] Azurocidin , a multifunctional protein has notable antimicrobial properties, particularly against Gram-negative bacteria.[106,107] Although, Azurocidin does not exhibit direct bactericidal activity against certain bacteria like *Capnocytophaga sputigena* but can synergize with other enzymes such as elastase and cathepsin G to enhance their bactericidal effects.[108] Beyond its direct antimicrobial effects, azurocidin acts as an immune system alarm, enhancing cytokine release, bacterial phagocytosis and chemotaxis of monocytes and macrophages. This makes it a significant mediator in the immune response.[109,110] The positively charged amino acids in azurocidin allow it to interact with the lipid A component of lipopolysaccharides (LPS) on bacterial surfaces. This binding is particularly strong under acidic conditions, such as those found in phagolysosomes within leukocytes, where the protein aids in bacterial killing.[111] Recent research indicates that azurocidin activates macrophages through β2-integrins, leading to the release of pro-inflammatory cytokines like tumor necrosis factor-alpha (TNF-α) and interferon-gamma (IFN-γ).[109] This activation enhances the expression of Fc receptors, enhancing the phagocytosis of IgG-opsonized bacteria. Although azurocidin's role in killing mycobacteria is not fully understood, studies suggest that azurophilic granule proteins, including azurocidin, are more effective against mycobacteria than other neutrophil granule proteins.[112] They also promote the fusion of mycobacteria-containing phagosomes with lysosomes. However, the exact mechanism by which azurocidin contributes to the intracellular killing of mycobacteria by leukocytes remains unclear.[112] Azurocidin shows promise as a therapeutic agent in tuberculosis due to its immunomodulatory properties and ability to promote intracellular killing of certain bacteria, including mycobacteria. However, further research is needed to fully understand its mechanisms and optimize its use in TB treatment.

Mycobacteriophage-derived peptide

Mycobacteriophages, the viruses that target mycobacteria, are emerging as a rich source of novel peptides with significant potential for TB treatment.[113] These peptides not only directly attack M.tb but also possess unique immunomodulatory abilities, making them compelling candidates in the fight against TB.[113]. Among these, peptides AK15 and its isomer AK15-6 have shown remarkable efficacy by binding to trehalose 6,6'-dimycolate (TDM), a key component of the mycobacterial cell wall, leading to the disruption of bacterial membranes. In addition to their antimicrobial action, these peptides also fine-tune the immune response, reducing excessive inflammation by inhibiting certain proinflammatory cytokines while still triggering the production of TNF-α and IL-6 in macrophages and T-cells.[114] Similarly, peptide PK34 exhibits a dual function, both killing M.tb and binding to TDM. What sets PK34 apart is its ability to dampen inflammation by deactivating MAPK and PKB signaling pathways, while still allowing some level of proinflammatory cytokine production.[115] These findings highlight the potential of mycobacteriophage-derived peptides as innovative tools in TB therapy, offering a one-two punch by directly targeting the bacteria and modulating the host's immune response.

Synthetic antimicrobial peptides against M.tb

In the face of rising multidrug-resistant TB, researchers are turning to synthetic antimicrobial peptides as a new frontier in TB treatment, unveiling a series of promising discoveries. Thymopentin (TP-5), a synthetic peptide composed of 5 amino acids - Arg-Lys-Asp-Val-Tyr - mimic the 32-36 amino acid sequence of the thymus hormone thymopoietin.[116] TP5 with strong immunomodulatory activities effectively treats primary and secondary immunodeficiencies, autonomic immunodeficienciesand severe infections in various animal models and human cell studies.[117–119] Modified immunomodulatory peptides RR-11 and RY-11, derived from thymopentin, exhibit potent anti-mycobacterial activity, disrupting bacterial membranes and enhancing immune response without toxicity. RY-11 also synergizes with rifampicin, reducing its effective dose and preventing resistance, showing promise for TB treatment in both immunocompetent and immunocompromised patients.[120] Thymopentin combined with anti-TB drugs significantly enhances the treatment of drug-resistant pulmonary TB, increasing sputum culture-negative rates, focal absorptionand shortening cough remission time. It also improves immune response by elevating $CD3^+$ and $CD4^+$ T cell levels while reducing $CD8^+$ T cells, demonstrating its potential as an effective adjunctive therapy.[121] Thymopentin (TP-5) and its modified derivatives, RR-11 and RY-11, show strong immunomodulatory and anti-mycobacterial properties, making them promising adjuncts in the treatment of drug-resistant pulmonary TB. Their ability to enhance immune response, improve treatment outcomesand synergize with rifampicin highlights their potential for broader therapeutic applications, especially in challenging TB cases. D-LAK peptides, composed entirely of D-amino acids, are another breakthrough. These peptides tackle MDR and XDR strains of Mycobacterium tuberculosis by breaking down bacterial clumps and disrupting their hydrophobic interactions. Although they didn't completely eradicate intracellular bacteria, they significantly curbed the growth of resistant strains and paired well with isoniazid, potentially enhancing its penetration into the bacteria.[122] In a different vein, IDR peptides - designed more for their immune-boosting than direct antimicrobial effects - showed their mettle against TB. IDR-1 peptides, like IDRHH2, IDR-1002and IDR-1018, though modest in direct antimicrobial action, dramatically reduced bacterial loads and lung inflammation in mice, even against MDR strains. Interestingly,

Table 1: List of antimicrobial peptides with immunomodulatory effects against tuberculosis.

AMPs	Source	Immunomodulatory function	References
Lactoferrin	Mammalian secretions like saliva, tears and milk	promotes Th1 response Boosts IFN-γ & IL-17 production	58, 61,68
LL-37	Predominantly human macrophage and neutrophils	TLR-9 activation Increases pro-inflammatory cytokines like IL-1β and TNF-α	76-79
WBCATH	Cathelicidin derived from water buffalo	synergistic effect with first-line antibiotics. Enhancing cytokine production in infected macrophages	83
Glutoxim	Tripeptide derivative of oxidized glutathione	Modulates intracellular thiol metabolism Activates cytokine systems Enhances phagocytosis	86-88
Thymopentin RR-11 and RY-11	Thymus hormone Modified derivatives of thymopentin	Modulate the production of various cytokines, such as interleukins and interferons. Induce protective T-cell response.	114-119
Defensins	Epithelial cells and neutrophils.	Adjunct effect with anti-TB drugs Effective against drug-resistant TB Immunomodulatory activity	92,95,97
Azurocidin	azurophilic and secretory granules of neutrophils.	Induce pro-inflammatory cytokines like TNF-α and IFN-γ	104-108
AK15, PK34	Mycobacteriophagederived peptide	Disrupting the bacterial membrane and Bind to trehalose 6,6-dimycolate (TDM), Synergy with rifampicin Regulate Inflammation by MAPK and PKB signaling	111-113
IDRHH2, IDR-1002and IDR-1018	Synthetic antimicrobial peptides	Reduce lung inflammation in mice, Active against MDR strains anti-inflammatory properties	122
IP-1	Synthetic antimicrobial peptides	induces autophagy in mammalian cells and macrophages enhances TNF-α secretion effective against MDR strain of TB	123
Magainin-I analog peptide	Synthetic antimicrobial peptides	Promote phagosome-lysosome fusion and apoptosis	124
M(LLKK)2M	Synthetic antimicrobial peptides	synergized with rifampicin, boosting its efficacy and delaying resistance	125

IDR-1018 also showcased anti-inflammatory properties in other models, hinting at its versatility as a potential immunotherapy for TB and beyond.[123] In a different vein, IDR peptides - designed more for their immune-boosting than direct antimicrobial effects - showed their mettle against TB. IDR-1 peptides, like IDRHH2, IDR-1002and IDR-1018, though modest in direct antimicrobial action, dramatically reduced bacterial loads and lung inflammation in mice, even against MDR strains. Interestingly, IDR-1018 also showcased anti-inflammatory properties in other models, hinting at its versatility as a potential immunotherapy for TB and beyond.[124] The synthetic peptide IP-1 (KFLNRFWHWLQLKPGQPMY) shows promise as a treatment for multi-drug resistan strains of M.tb. IP-1 induces autophagy in mammalian cells and macrophages at low dosesand at higher doses, it has bactericidal activity and induces cell death. It also reduces intracellular ATP levels and enhances TNF-α secretion, which helps eliminate MDR MTB. IP-1 effectively clears MTB in vitro and shows significant therapeutic activity in a murine model of progressive pulmonary TB, suggesting its potential as a combined antimicrobial and autophagy-inducing treatment for resistant infection.[125] To tackle delivery challenges, nano-encapsulated Magainin-I analog peptide (MIAP) using Porous Nanoparticle Aggregate Particles (PNAP) is studied. This formulation not only improved lung delivery and stability but also demonstrated strong antibacterial action, significantly lowering bacterial counts. MIAP-PNAP also enhanced host defenses by promoting phagosome-lysosome fusion and apoptosis, making it a promising adjunct therapy for TB.[126] Lastly, a study on synthetic cationic α-helical AMPs modified with hydrophobic amino acids revealed an innovative approach to TB treatment. By adding methionine residues, the researchers amplified the peptides' effectiveness against drug-susceptible and drug-resistant TB strains, including multidrug-resistant variants. The optimized peptide, M(LLKK)2M, showed a powerful membrane-lytic action, effectively eradicating mycobacteria without resistance development. Moreover, it synergized with rifampicin, boosting its efficacy and delaying resistance, pointing to its potential as a game-changing tool against TB.[127] Together, these studies illustrate the exciting potential of synthetic antimicrobial peptides in transforming TB treatment, offering new hope against even the most resistant strains.

DISCUSSION

Although many antimicrobial peptides are produced naturally in the body, they are often insufficient to clear certain pathogens, particularly intracellular ones like M.tb. Initial findings indicate that M.tb infections can down-regulate the expression of these cationic peptides and hinder their activation.[128] Consequently, to effectively kill these pathogens, external administration or hormonal induction of peptide synthesis may be necessary.[129] For instance, a significant reduction in M.tb load has been observed both in vitro and in vivo following the exogenous addition of

purified cathelicidin.[130] Furthermore, inducing the expression of the cathelicidin-encoding gene using vitamin D has also shown effectiveness. Recent studies have demonstrated that administering a combination of 500 mg Polybutyrate and 5000 IU vitamin D3 significantly boosts Cathelicidin synthesis, leading to the intracellular killing of M.tb by macrophages.[131,132] This drug combination has the potential to enter into clinical trials for the treatment of active tuberculosis in adults.[133] While many AMPs show great potential as therapeutic agents, only a few have progressed to clinical trials. For instance, the lactoferrin derivative hLF-11 has shown effectiveness against multi-drug resistant *Staphylococcus aureus* (MRSA) and has entered phase I clinical trials for treating common hospital infections.[134] Likewise, a cathelicidin derived from snake venom, known for its antimicrobial and anti-inflammatory properties, is being used therapeutically against acne vulgaris.[135] In a nutshell, antimicrobial peptides are among the most ancient components of the immune system, providing defense against invading pathogens. Host-directed immunomodulatory therapies using AMPS show promise in enhancing protective antimycobacterial immunity while limiting inflammation-induced tissue injury, offering a promising new approach for treating M.tb infections. Further research on antimicrobial peptides in the context of TB is essential. In the future, advancements in recombinant production methods, which could significantly reduce production costs, along with protein modifications to enhance stability and reduce cytotoxicity, may encourage researchers and pharmaceutical companies to develop novel AMP-based therapeutics.

CONCLUSION AND OUTLOOK

The rise of drug-resistant M.tb has underscored the urgent need for novel therapeutic agents. Recent research is focused to AMPs that exhibit broad-spectrum activity against pathogens, including M.*tb* and play a crucial role in immune modulation. These peptides, with their unique structural features, offer promising scaffolds for the development of new drugs. Their capacity to target drug-resistant M.tb strains makes them promising candidates. Although, AMPs show potential in tackling global antimicrobial resistance several challenges make their use in medicine difficult. These challenges include their vulnerability to being broken down by proteases, high production costs, lack of specificity, toxicity to cells, poor absorption and short lifespan in the body. Additionally, bacteria can develop resistance to AMPs, a problem that isn't yet fully understood, making it a significant barrier to their clinical use. However, although many AMPs are in clinical trials, only a few have reached the market due to issues like poor drug behavior in the body and other complications. More research is needed to understand how bacterial membranes contribute to this resistance. Despite these challenges, AMPs have properties that help reduce the development of resistance in M.tb. They can also work well when combined with existing anti-TB drugs to improve treatment effectiveness. Techniques like encapsulation, where AMPs are enclosed in nanomaterials, could help protect them from degradation and improve their stability and effectiveness. While several AMPs are progressing through clinical trials, much work remains to develop AMP-based therapies that are safe, effective and specifically targeted for tuberculosis treatment.

Abbreviations:

M.tb: Mycobacterium tuberculosis
TB: Tuberculosis
ATT: Anti-Tuberculosis Therapy
MDR: Multidrug-Resistant
XDR: Extensively Drug-Resistant
BCG: Bacille Calmette-Guérin
AMPs: Antimicrobial peptides
DCs: Dendritic Cells
Th1: T-cell helper 1
TLR: Toll-like receptor
LPS: Lipopolysaccharides
HβD: Human β-defensin
PMN: Polymorphonuclear
HBP: Heparin-binding protein
TNF-α: Tumor necrosis factor-alpha
IFN-γ: Interferon-gamma
TDM: Trehalose 6,6-dimycolate
TP-5: Thymopentin
MIAP: Magainin-I analog peptide
PNAP: Porous Nanoparticle Aggregate Particles
MRSA: Multi-drug resistant Staphylococcus aureus

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ETHICAL APPROVAL

Not applicable

CONFLICT OF INTEREST STATEMENT

The authors declare that there is no conflict of interest for publication of this review work.

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