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Review

Host-Directed Therapeutics as a Novel Approach for Tuberculosis Treatment

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Despite significant efforts to improve the treatment of tuberculosis (TB), it remains a prevalent infectious disease worldwide owing to the limitations of current TB therapeutic regimens. Recent work on novel TB treatment strategies has suggested that directly targeting host factors may be beneficial for TB treatment. Such strategies, termed host-directed therapeutics (HDTs), focus on host-pathogen interactions. HDTs may be more effective than the currently approved TB drugs, which are limited by the long durations of treatment needed and the emergence of drug-resistant strains. Targets of HDTs include host factors such as cytokines, immune checkpoints, immune cell functions, and essential enzyme activities. This review article discusses examples of potentially promising HDTs and introduces novel approaches for their development.

Keywords: Tuberculosis, *Mycobacterium tuberculosis,* multidrug resistance, host-directed therapeutics, immunomodulatory regulator
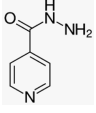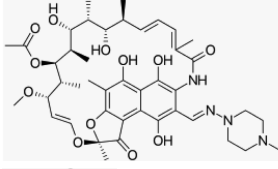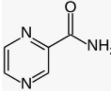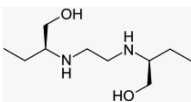
Introduction
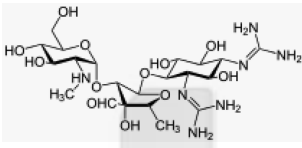
Tuberculosis (TB), which is caused by infection with *Mycobacterium tuberculosis* (MTB), is a global health problem with significant lethality [1]. In 2015, 10.4 million people were infected with TB, and 1.8 million people died because of the disease, including 0.4 million people who were coinfected with human immunodeficiency virus (HIV). This is significant because in that same year, 35% of HIV-related deaths were caused by TB. In 2015, approximately 480,000 people had multidrug-resistant TB (MDR-TB), and 9% of TB patients were infected with an MTB strain that was classified as extensively drug-resistant TB (XDR-TB). Treatment of these resistant strains requires a considerably long duration, with toxic side effects and at a great expense [2]. For the past 40 years, TB therapy has used a combination of effective anti-TB drugs to manage acti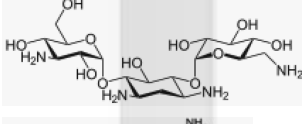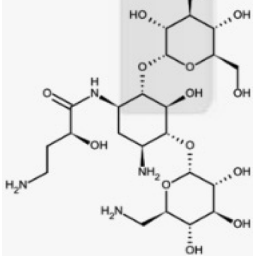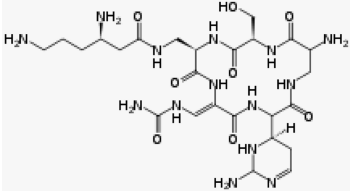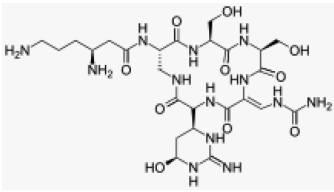ve infections. Generally, TB needs to be treated for 6 months and XDR-TB for 12–18 months. Furthermore, the current therapy for XDR-TB is effective in only 50% of cases and imposes a severe financial burden on patients [3]. Current anti-TB drugs have other limitations such as adverse effects and interactions with other drugs [4]. In addition, patients experience abnormal host inflammatory responses caused by permanent lung tissue damage [5]. Therefore, novel therapeutic strategies are required to treat these difficult TB cases. One novel approach, termed host-directed therapeutics (HDTs), involves directly targeting host factors rather than pathogen components [6]. HDTs also reduce pathogen proliferation and the hyperinflammatory response by modulating the host immune system [7]. HDTs have improved clinical outcomes with reduced morbidity, mortality, organ damage, and TB therapy duration.
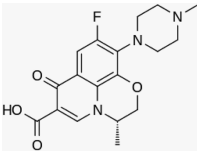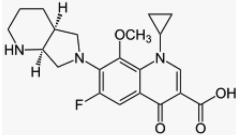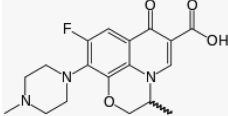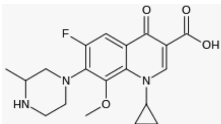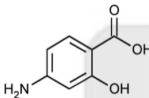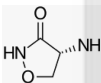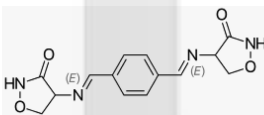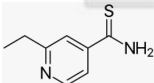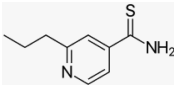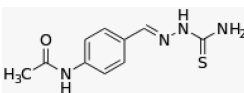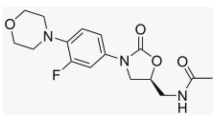
Current Anti-TB Drugs

Treatment with first-line anti-TB drugs (Table 1) is a two-step process that was developed from 1950 to 1960; treatment lasts for at least 6 months [8]. The first step is an intensive treatment over 2 months with four first-line drugs: isoniazid (4-pyridinecarboxylic acid hydrazide**,** INH), rifampicin, pyrazinamide, and ethambutol. The second step is 4 months long and involves continuous isoniazid and rifampicin administration (short-course chemotherapy) [9].

Table 1. Current drugs for treatment of tuberculosis (TB).

Classification	Drug name	Year of discovery	Group	Structure
First-line anti-TB drugs	Isoniazid	1952	Group1 : Oral	
	Rifampicin	1963		
	Pyrazinamide	1954		
	Ethambutol	1961		
Second-line anti-TB drugs	Streptomycin	1944	Group 2 : Injectable aminoglycosides	
	Kanamycin	1957		
	Amikacin	1972		
	Capreomycin	1963	Group 2 : Injectable polypeptides	
	Viomycin	1951		
	Ciprofloxacin	1961	Group 3 : Oral and injectable fluoroquinolones	

Table 1. Continued.

Classification	Drug name	Year of discovery	Group	Structure
Second-line anti-TB drugs	Levofloxacin	1987	Group 3 : Oral and injectable fluoroquinolones	
	Moxifloxacin	1988		
	Ofloxacin	1980		
	Gatifloxacin	1992		
	Para-aminosalicylic acid	1948	Group 4 : Oral	
	Cycloserine	1954		
	Terizidone	1965		
	Ethionamide	1961		
	Prothionamide	1956		
	Thioacetazone	1951		
	Linezolid	1996		

Anti-TB drugs are categorized by evidence of efficacy, potency, and case of use.

INH targets an enoyl-(acyl-carrier-protein) reductase and inhibits mycolic acid synthesis; it is a prodrug that requires activation by the catalase-peroxidase enzyme KatG [10]. Pyrazinamide inhibits translation by inhibiting the 30S ribosomal S1 component [11]. First-line drugs such as INH and pyrazinamide contribute to host defenses against MTB by triggering the formation of cellular and mitochondrial reactive oxygen species (ROS) and activating autophagy, which reduces the MTB-induced proinflammatory response in macrophages [12, 13]. Ethambutol targets arabinosyl transferase, which blocks arabinogalactan biosynthesis [14]. Although these first-line drugs initially show anti-TB

effects, they have several limitations. These TB treatment regimens are lengthy, involve drug intolerance and toxicity, and require the consideration of pharmacokinetic drug-drug interactions, particularly with anti-HIV drugs for patients with HIV coinfection [4]. The development of an improved TB therapeutic approach that is shorter, more effective against resistant strains, and has fewer drug interactions is needed [15]. Drug resistance to MTB is typically caused by inappropriate treatment of active TB infections [16].

MDR-TB is characterized by resistance to isoniazid and rifampicin. XDR-TB is defined as TB that is resistant to both isoniazid and rifampicin, as well as to any fluoroquinolone and at least one of the second-line injectable drugs (capreomycin, kanamycin, and amikacin) [17]. A World Health Organization TB treatment report has recommended treating MDR/XDR-TB using a combination of four or more anti-TB drugs that are effective against MTB [18].

Second-line anti-TB drugs are used to treat MTB infections that are resistant to first-line drugs (Table 1: Groups 2, 3, and 4). Group 2 contains injectable anti-TB drugs. Streptomycin is an aminoglycoside antibiotic, derived from the soil microorganism *Streptomyces griseus*, which is used to treat many bacterial infectious diseases, including TB [2]. This drug was the first antibiotic used against TB. Streptomycin interacts directly with the 12S and 16S rRNA components of the 30S ribosomal subunit, thus inhibiting protein synthesis [19]. Unfortunately, the use of this antibiotic led to the rapid emergence of a resistant strain [20]. Because many MDR-TB patients have resistance to streptomycin, it is not commonly used for treating MDR-TB [21]. Second-line anti-TB drugs such as kanamycin, amikacin, capreomycin, and viomycin target protein synthesis. Kanamycin and amikacin are aminoglycosides and target the 30S ribosomal subunit [22]. Capreomycin and viomycin are cyclic peptide antibiotics with similar structures that bind at the same site on the ribosome. They target the interface between the 30S and 50S ribosomal subunits. However, Group 2 drugs also cause several adverse effects such as ototoxicity, neurotoxicity, nephrotoxicity, and hypersensitivity. In particular, aminoglycosides may act as neuromuscular blocking agents, leading to respiratory failure [23]. Group 3, composed of fluoroquinolones, inhibits topoisomerase II (DNA gyrase), topoisomerase IV, and MTB topoisomerase II [24]. The side effects of fluoroquinolones occur mainly in the gastrointestinal tract, and 3–17% of patients treated with fluoroquinolones experience these side effects [23]. Group 4, oral bacteriostatic second-line anti-TB drugs, includes para-amino salicylic acid (PAS), cycloserine, ethionamide, and linezolid. PAS targets dihydropteroate synthase, causing it to inhibit folate biosynthesis and iron uptake [25]. Common adverse effects of PAS include nausea, pain, and diarrhea. PAS can also cause liver inflammation and other allergic reactions [26]. Cycloserine, a D-alanine analog, inhibits peptidoglycan synthesis [27] and can have neurological and psychiatric side effects. [23] Ethionamide is a potent drug used to treat MDR-TB, and its structure is similar to that of isoniazid. It is also a prodrug that requires activation by a monooxygenase encoded by the *eth*A gene [28]. Similar to isoniazid, ethionamide targets an enoyl-(acyl-carrier-protein) reductase and inhibits mycolic acid biosynthesis [29]. It can also lead to adverse effects in the gastrointestinal tract, along with hepatotoxicity, neurotoxicity, cardiovascular effects, and endocrine effects [23]. Linezolid (Zyon) is a representative drug for eradicating resistant strains. Linezolid was approved for use against drug-resistant, gram-positive bacteria in the 2000s [30]. It is a member of the oxazolidinone antibiotic class, and inhibits protein synthesis by interfering with the functioning of the 23S rRNA. In addition, linezolid has in vitro antibacterial activity against MTB, including against MDR and XDR strains [31]. Moreover, linezolid had an effect on XDR strains in a study on pulmonary-TB patients [32] (Table 1). Linezolid therapy can last for less than 28 days and has mild side effects. This drug affects the nervous, gastrointestinal, hematologic, hepatic, and metabolic systems [33]. Second-line anti-TB drugs, which are used to treat infections resulting from a first-line drug-resistant strain, have also led to the development of resistant MTB strains. A spontaneous mutation in a MTB gene targeted by a current TB drug can result in drug resistance.

The Need for Novel TB Drugs

New drugs for treating MDR-/XDR-TB would ideally have a novel mechanism of action to circumvent the current drug resistance. Lower toxicity drugs could reduce side effects during TB treatment. The period of treatment, which imposes a considerable economic burden and is associated with the risk of the development of antibiotic-resistant strains, also needs to be shortened. To shorten the treatment period, novel drugs should have potent bactericidal activity against most types of MTB. Novel drugs should be effective and safe, and a low dosage frequency would also be promising. Therefore, the development of dose formulations and delivery technologies is another requirement for more advanced TB treatment. Effective drug combination regimens can also reduce the number of pills required [17].

Host-Directed Therapies

HDTs for managing TB are composed of two main strategies: enhancing the antimicrobial activity to clear pathogens, and controlling excess inflammation to prevent permanent lung tissue damage. Current HDTs can potentially inhibit TB development via diverse host pathways, such as signal transduction-mediating cytokines, antimicrobial processes, immune cell regulation, and epigenetic modulation [34]. The use of HDTs can be expected to reduce the bacterial burden and fine-tune the host inflammatory response. HDTs may also require minimal doses and short treatment durations and may be used in combination with existing drugs to enhance their overall effect.

Next, this review introduces several representative HDTs

for the treatment of TB (listed in Table 2) [34].

(1) Metformin (Glucophage), which acts as an autophagy inducer, is currently approved for the treatment of type 2 diabetes. Many studies have shown that the activation of autophagy leads to the clearance of MTB [35]. Metformin activates adenosine monophosphate-activated protein kinases, which are sensors of cellular energy levels [36]. Targeting adenosine monophosphate-activated protein kinases is predicted to be a potential anti-TB treatment [37]. Metformin inhibits MTB growth by inducing mitochondrial ROS production in vitro. The effect of current anti-TB drugs can be enhanced by metformin, which was confirmed in both acute and chronic TB mouse models. Furthermore, metformin reduced the TB-mediated tissue pathology and enhanced interferon (IFN)-γ-secreting CD8+ and CD4+

Table 2. Development of host-directed therapeutics for tuberculosis.

Category	Name	Currently approved indication(s)	Host target	Developmental stage	Ref.
Repurposed drug	Imatinib	Leukemia and gastrointestinal stromal tumors	Tyrosine kinase	Preclinical/clinical (early phase)	[39]
	Verapamil	High blood pressure, chest pain and supraventricular tachycardia	Voltage-dependent calcium channels		[34]
	Metformin	Diabetes	AMP-activated protein kinase activator		[38]
	Ibuprofen	Pain and fever relief	Cyclooxygenase inhibitor		[41]
Cytokine therapy	IL-2	Renal cancer and melanoma	Cytokine modulation	Clinical (late phase)	[53]
	GM-CSF	Acute myelogenous leukemia, after bone marrow transplantation	Cytokine modulation		[64]
	IFN-γ	Chronic granulomatous disease	Cytokine modulation		[65]
Monoclonal antibody	Adalimumab (Anti-TNFα)	Rheumatoid arthritis	Cytokine neutralization	Preclinical/ clinical (early phase)	[54]
	Tocilizumab (Anti-IL6R)	Juvenile arthritis, Castleman's disease	Cytokine neutralization		[56]
	Bevacizumav (Anti-VEGF)	Various cancer types	Angiogenesis inhibitor		[57]
Monoclonal antibody	Nivolumab /pembrolizumab (Anti-PD-1)	Melanoma, various other cancers	Immune checkpoint inhibitor	Preclinical	[45]
	Anti-LAG3	Various cancers	Immune checkpoint inhibitor		[66]
	Ipilimumab (Anti-CTLA-4)	Melanoma, various other cancers	Immune checkpoint inhibitor		[67]
Vitamin	Vitamin D$_3$	Dietary supplement	Innate immune response activator	Clinical (late phase)	[44]
Cellular therapy	Bone marrow-derived mesenchymal stromal cells	Various inflammatory indications	Reduction of inflammation and enhancement of tissue regeneration	Clinical (late phase)	[68]
	Antigen-specific T cells	Cancer and viral infections	Targeted killing of MTB-infected host cells		[68]

T-cell populations. It also reduced the activity of chronic inflammatory genes in TB patients, in addition to reducing mortality [38].

(2) Imatinib mesylate (Gleevec) is used to treat leukemia and gastrointestinal stromal tumors. Imatinib is a small-molecule kinase inhibitor that blocks tyrosine kinase enzymes. The therapeutic administration of imatinib promotes the acidification and maturation of MTB-infected macrophage phagosomes, reducing the number of colony-forming units (CFUs) in MTB-infected mice. Furthermore, imatinib works synergistically with first-line anti-TB drugs to inhibit drug-resistant mycobacterial strains. At subtherapeutic concentrations, imatinib strengthens host defenses by increasing neutrophil and monocyte numbers through myeloproliferation [39, 40].

(3) Ibuprofen (Advil, Motrin, Nurofen) is a non-steroidal anti-inflammatory drug normally used as a painkiller and an antipyretic. This inhibitor of cyclooxygenase inhibits prostaglandin E_2 production and enhances tumor necrosis factor (TNF) production in macrophages. Although the direct antimycobacterial activity of ibuprofen is not potent, it reduces lung tuberculous lesions and bacterial burden and enhances the survival rate in a mouse model that mimics active TB [41].

(4) Zileuton (ZYFLO) is a 5-lipooxygenase inhibitor that inhibits the formation of leukotrienes (LTB4, LTC4, LTD4, and LTE4) and has been approved to treat asthma. Mice and humans infected with MTB show decreased IL-1 responses and increased production of type I IFN, resulting in an eicosanoid imbalance that causes severe TB. Zileuton reduces weight loss and the number of CFUs and protects against acute mortality by increasing prostaglandin E_2 levels [42].

(5) Vitamin D_3 is a dietary supplement that activates the innate immune response. Low vitamin D_3 levels are involved in the development of active TB. Vitamin D_3 has an important role in converting 2,5(OH)D into 1,25-$(OH)_2D_3$, which is its active form. This active form induces the production of cathelicidin, which is an antimicrobial peptide. After MTB infection, macrophages produce cathelicidin through Toll-like receptor signaling; thus, vitamin D can indirectly inhibit MTB [43]. Treatment with both vitamin D_3 and 4-phenyl butyrate synergistically enhances cathelicidin production [44].

(6) Another potent target of HDTs is immune checkpoints. These immunomodulatory therapeutic strategies have been studied extensively in cancer research. Programmed cell death 1 (PD-1) is a protein on the surface of active T cells. When programmed death-ligand 1 (PD-L1) and PD-L2

associate with PD-1 on the T-cell surface, T cells cannot attack other cells. Nivolumab and pembrolizumab are PD-1 inhibitors currently used to treat melanomas and other cancers. Antigen-specific IFN-γ was rescued using a PD-1 inhibitor in TB patients, confirming that nivolumab/pembrolizumab has potential in treating TB [45]. Cytotoxic T-lymphocyte-associated protein 4 affects immune checkpoints, and it is expressed in active TB patients. Antigen-specific lymphocyte expansion and cytokine expression can be increased by blocking cytotoxic T-lymphocyte-associated protein 4 [46].

(7) Cytokine therapy could be an alternative method to limit the currently used TB chemotherapy. This method uses immunomodulators to boost the immune system [47]. Cytokines contribute to various cellular responses, including immune signaling in TB. Cytokine therapy induces a proinflammatory immune response and antimicrobial activity, which can be beneficial in treating TB. IFN-γ plays a major role in the host defenses against MTB. IFN-γ, as a prototypical product of Th1 cells, promotes the secretion of Th1 cytokines (such as IL-12) and inhibits Th2 cytokines (such as IL-4). In addition, IFN-γ upregulates class I and II antigen-presenting cells and increases the antimicrobial activity of macrophages. Mutations in the IFN-γ receptor gene result in high susceptibility to mycobacterial infections [48]. Granulocyte macrophage colony-stimulating factor (GM-CSF) increases the number of macrophages, leading to an enhanced inflammatory response. GM-CSF also shows antimycobacterial activity in human macrophages [49]. Studies on GM-CSF-deficient mice showed that GM-CSF plays critical immunomodulatory roles in the host defenses against pulmonary TB [50]. Moreover, IL-2 induces the expansion of T cells. However, recent studies have shown that IL-2 promotes CD4+CD25+ regulatory T-cell expansion, which suppresses the T-cell response [51]. Some clinical trials testing the effectiveness of IL-2 against TB have been reported [52, 53].

Excessive proinflammatory cytokine production causes permanent host tissue damage. Therefore, regulating cytokine production could be an alternative approach to treat TB by reducing destructive inflammation. The current monoclonal antibody used for cytokine neutralization modulates inflammatory responses. The anti-TNF therapeutic agent adalimumab has been previously used to treat TB [54]. IL-6, which accelerates the severity of disease in TB patients, is a promising candidate. Blockage of the IL-6/IL-6 receptor pathway is considered therapeutic in treating various diseases [55]. The use of a monoclonal antibody, along with the IL-6 receptor blockage, enhances anti-TB

T-cell responses, decreases severe pathology, and reduces the MTB burden in mice [56]. The anti-vascular endothelial growth factor (anti-VEGF, bevacizumab) monoclonal antibody inhibits TB by normalizing vasculature, increasing the delivery of small molecules, and decreasing hypoxia in tuberculous granulomas [57]. Therefore, the anti-VEGF monoclonal antibody may increase the efficacy of current treatment regimens.

Cell-based therapies are considered effective alternative therapies in treating cancer and infectious diseases. In addition, such therapies might decrease tissue-destructive inflammation, enhance organ repair, and intensify antigen-specific immune responses [58].

Several studies have focused on immunomodulatory functions that show antimycobacterial activity [59−61]. Previously, we developed a novel treatment strategy for treating an intracellular parasite infection, which might be used as an HDT strategy against TB. We investigated interactions between the intracellular parasite *Toxoplasma gondii* and host macrophages and clarified the cellular signaling involved in this interaction. *T. gondii* dense granule antigen (GRA) 7 is essential for the innate immune response and acts through an association with TNF receptor-associated factor 6 (TRAF6) via myeloid differentiation primary response gene 88. The interaction between GRA7 and TRAF6 confers a protective effect against *T. gondii* infection in vivo [62]. We performed further experiments to determine whether GRA7 modulation of the innate immune response could work for other infectious diseases such as TB. We found that GRA7 interacted with many host proteins, including important host immune response regulators. We showed that the protein kinase C alpha-mediated phosphorylation of GRA7 is essential for the interaction between apoptosis-associated speck-like protein
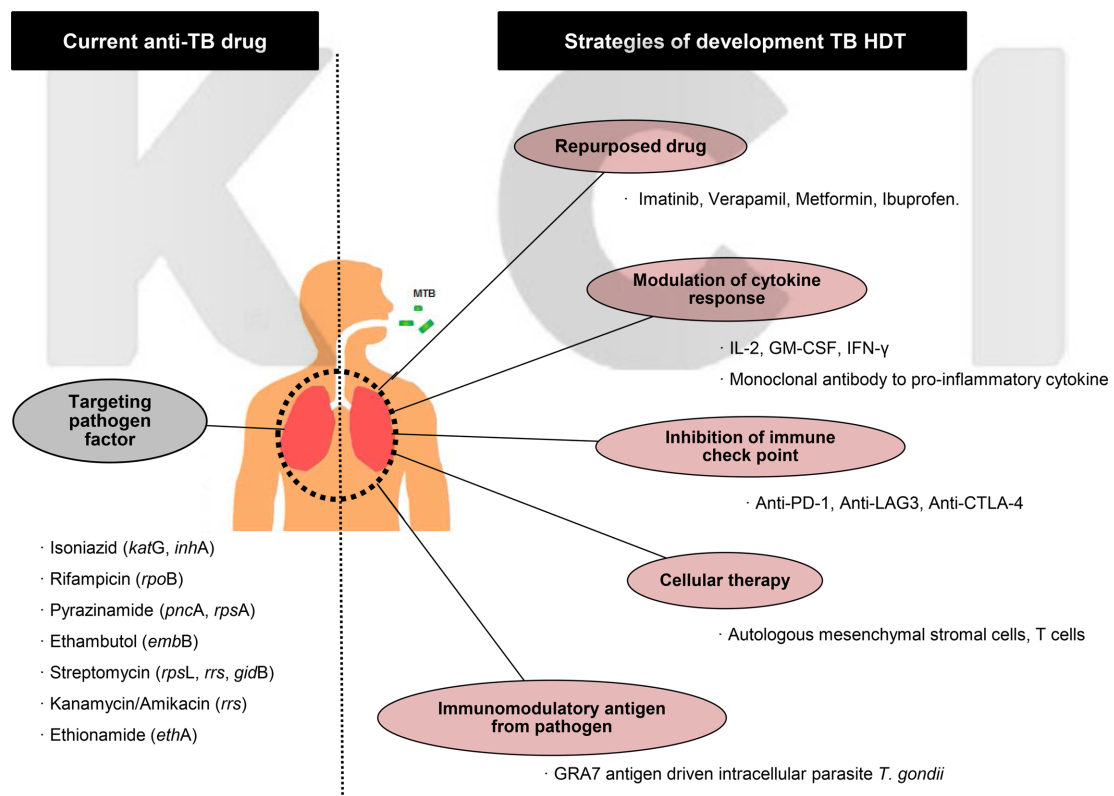
Fig. 1. Comparison between current anti-tuberculosis (TB) drugs and potential host-directed therapeutic (HDT) strategies for treating TB.

Current anti-TB drugs have been developed by targeting pathogenic factors such as bacterial proliferation. A spontaneous mutation in one of the genes that is targeted by these antibiotics can lead to the emergence of drug-resistant TB strains. To overcome the limitations of current anti-TB drugs, the development of new drugs is necessary. HDTs directly affect host factors. Strategies for developing anti-TB HDTs have been verified in several TB studies. IL-2, Interleukin-2; GM-CSF, Granulocyte macrophage colony-stimulating factor; IFN-γ, Interferon gamma; PD-1, Programmed cell death protein 1, LAG3, Lymphocyte activation gene 3; CTLA-4, Cytotoxic T-lymphocyte-associated antigen 4; GRA7, *Toxoplasma gondii* dense granule antigen 7.

containing a carboxyl-terminal CARD and phospholipase D1. These interactions induced antibacterial activity against TB. GRA7 controlled the innate immune response by interacting with host cell proteins. Our current studies have established proof of concept for developing novel HDT strategies that could serve as alternatives to treat TB [63] (Fig. 1).

In conclusion, by directly targeting host factors, HDTs enhance immune responses and fine-tune inflammation, and can thus be used to treat bacterial, viral, and parasitic infectious diseases. Current treatment for MTB-mediated TB has several limitations, including the long period of treatment, emergence of resistant strains, and toxicity of the drugs. These limitations increase the need for developing novel TB treatment strategies. The present review focused on potential novel HDTs that may be used to treat TB. HDTs play a role in the clearance of MTB and regulation of excess inflammatory responses to protect the host from permanent organ damage. Furthermore, the combination of HDTs with current TB drugs reduces drug dosages and improves clinical outcomes. HDTs can be used to target many pathways, and as such can be used to verify the antimycobacterial activity of an approved drug (re-purposed drugs), inhibit immune checkpoints, and modulate cytokine production. We have shown that antigens derived from the intracellular parasite *T. gondii* modulate the immune response and might be promising for treating MBT infection. However, the potential uses of HDTs need to be explored further. Because HDTs directly interact with host factors, various factors need to be considered prior to their application. Furthermore, it is difficult to establish HDTs that manipulate a human factor using animal models. Because HDTs target complex pathways, there should be detailed investigations into the potential side effects of HDTs. Understanding the host immune response in TB-mediated immune pathology is very important in HDT research.

Acknowledgments

Conflict of Interest

The authors have no financial conflicts of interest to declare.

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