INTRODUCTION

Tuberculosis (TB), caused by Mycobacterium tuberculosis (Mtb), remains a major health problem. With an estimated 10 million disease cases and 1.4 million deaths in 2019, Mtb is the deadliest infectious agent worldwide and TB is one of the top-10 leading causes of deaths globally.\(^1\) Approximately a quarter of the world’s population is infected with Mtb and in most cases, progression toward TB disease is prevented by an efficient host immune response, often resulting in a latent TB infection (LTBI).\(^2\) Five to fifteen percent of LTBI individuals will develop TB disease during their lifetime, often concomitant with host immunocompromising conditions, including HIV infection and use of immunosuppressive medication. Treatment of patients with active TB has largely remained unchanged for over 30 years,\(^3\) and due to its lengthiness (6-24 months) and considerable

Abstract

Upon infection, mycobacteria, such as Mycobacterium tuberculosis (Mtb) and nontuberculous mycobacteria (NTM), are recognized by host innate immune cells, triggering a series of intracellular processes that promote mycobacterial killing. Mycobacteria, however, have developed multiple counter-strategies to persist and survive inside host cells. By manipulating host effector mechanisms, including phagosome maturation, vacuolar escape, autophagy, antigen presentation, and metabolic pathways, pathogenic mycobacteria are able to establish long-lasting infection. Counteracting these mycobacteria-induced host modifying mechanisms can be accomplished by host-directed therapeutic (HDT) strategies. HDTs offer several major advantages compared to conventional antibiotics: (a) HDTs can be effective against both drug-resistant and drug-susceptible bacteria, as well as potentially dormant mycobacteria; (b) HDTs are less likely to induce bacterial drug resistance; and (c) HDTs could synergize with, or shorten antibiotic treatment by targeting different pathways. In this review, we will explore host-pathogen interactions that have been identified for Mtb for which potential HDTs impacting both innate and adaptive immunity are available, and outline those worthy of future research. We will also discuss possibilities to target NTM infection by HDT, although current knowledge regarding host-pathogen interactions for NTM is limited compared to Mtb. Finally, we speculate that combinatorial HDT strategies can potentially synergize to achieve optimal mycobacterial host immune control.

KEYWORDS

drug resistance, host-directed therapy, Mycobacterium avium, Mycobacterium tuberculosis, nontuberculous mycobacteria

1 | INTRODUCTION

This article is part of a series of reviews covering immunity to Mycobacteria appearing in Volume 301 of Immunological Reviews.

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side effects, treatment-adherence is low fueling development of multi-drug and extensive-drug resistance (MDR and XDR). The large TB disease burden and the increasing incidence of drug resistance make alternative treatment solutions imperative.

While the number of TB cases is slowly declining, a trend that may well be broken as a result of the COVID-19 pandemic, the prevalence of infections known to be caused by nontuberculous mycobacteria (NTM) is increasing at an alarming rate, currently reaching 0.2-9.8 per 100,000 individuals. NTM represent a group of opportunistic mycobacterial pathogens that mostly cause pulmonary diseases (PD), predominantly in vulnerable populations due to immunodeficiencies and/or pre-existing lung conditions. Mycobacterium avium (Mav) complex (MAC) and Mycobacterium abscessus (Mab) account for the large majority of reported cases. Despite extended treatment regimens, clinical outcome is poor, with cure rates of approximately 50%-88% among MAC-PD patients and 25%-58% among Mab-infected individuals, urging the development of novel treatment modalities.

Mycobacteria are well known for their capability to manipulate intracellular signaling pathways to escape from host-defense mechanisms in human cells. Mtb is best studied in this regard, but NTM have also been shown to modulate host immune responses, including preventing phagosomal acidification and maturation or escaping from phagosomes into the nutrient-rich cytosol. Counteracting pathogen-induced immune modulation by host-directed therapy (HDT) is a promising adjunct therapy to antibiotic therapy to combat intracellular mycobacterial infections, with several major advantages over current antibiotics. First, HDT can also be effective against MDR/XDR mycobacteria that are insensitive to current standard antibiotics. Second, because there is no direct selection pressure on mycobacteria, host-targeting compounds are less likely to result in drug resistance. Third, host-targeting compounds have the potential to target metabolically inactive, non-replicating bacilli during LTBI, which are tolerant or resistant to conventional therapies. Fourth, HDT may allow shortening of current lengthy TB/NTM-treatment regimens, thereby increasing compliance. Fifth, HDT may permit dose lowering of standard antibiotics, thus reducing toxicity without impacting efficacy. Finally, as HDT and mycobacterium-targeting compounds (ie, antibiotics) by definition act on different pathways, combinatorial regimens would be expected to synergize. In this review, we will provide a comprehensive overview of host-pathogen interactions that have been identified in Mtb infections and that are amenable to targeting by HDTs (summarized in Figure 1 and Table 1). Furthermore, despite a limited number of reports, we will also discuss NTM-mediated host modulation and speculate whether HDTs could also be of interest to combat these mycobacterial infections. Finally, we will discuss the possibility of combinatorial HDTs that target distinct host signaling pathways to promote possible synergistic treatment effects.

2 | HDT MODULATING INNATE IMMUNE CELL FUNCTION

2.1 | Phagocytosis and phagosome maturation

The first potential target for HDT to interfere with host-pathogen interactions is to modulate mycobacterial host-cell entry. Mycobacteria infect host cells, predominantly alveolar macrophages and epithelial cells, in the lower respiratory tract, following inhalation of small bacteria-containing aerosols. Mycobacteria express pathogen-associated molecular patterns (PAMPs) that are recognized by pattern recognition receptors (PRRs), such as Toll-like receptors (TLRs), C-type lectin receptors, and other scavenger receptors expressed on the surface of host cells to initiate phagocytosis. Especially TLR2, which forms heterodimers with TLR1 and TLR6 to recognize lipopeptides (eg, lipomannan), and TLR4, which recognizes cell wall lipids, glycoproteins, and secreted proteins, are known to mediate Mtb-induced cellular activation. Mice lacking TLR2 are more susceptible to infections with virulent Mtb and Mav strains.
NTM, including *Mav* and *Mab*, express a class of glycolipids known as glycopeptidolipids (GPLs) which mask underlying cell wall phosphatidyl-myo-inositol mannosides, thereby limiting interactions with TLR2. Moreover, the acetylation state of lipomannan modulates TLR2-mediated macrophage activation, and subversion of the TLR2-MyD88 pathway has been linked to phagolysosome escape of virulent *Mtb* to the cytosol, indicating a crucial role for TLR signaling pathways in the control of intracellular mycobacteria. Several PRR agonists, including TLR2 agonist Pam2Cys, have been identified that activate both innate and adaptive immune responses against...
| Compound                  | Biological activity                        | Model     | Pathogen | Reference |
|---------------------------|-------------------------------------------|-----------|----------|-----------|
| Phagocytosis and phagosome maturation |                                | In vitro | Mtb      | 13-17     |
| PRR agonists              | ↑ PRR-signaling                           | In vitro | Mtb      | 19        |
| miRNA-125 inhib.          | ↑ TLR2-signaling                          | In vitro | Mtb      | 20        |
| miRNA-23a-5p inhib.       | ↑ TLR2-signaling                          | In vitro | Mtb      | 26,27     |
| Imatinib                  | ↑ Phagosomal acidification                 | In vitro | Mtb, Mm  | 28        |
| AZD0530                   | ↑ Phagosomal acidification                 | In vivo   | Mtb      | 28        |
| AT9283                    | Unknown                                   | In vitro | Mtb      | 29        |
| ENMD-2076                 | Unknown                                   | In vitro | Mtb      | 29        |
| Dovitinib                 | Unknown                                   | In vitro | Mtb      | 29        |
| Nitazoxanide              | ↑ Cytoplasmic pathogen recognition        | In vitro | Mtb      | 33,34     |
| Metformin                 | ↑ Phagosome maturation                    | In vitro | Mtb      | 75-77     |
| Gefitinib                 | ↑ Lyosomal biogenesis                     | In vitro | Mtb      | 78        |
| Bedaquiline               | ↑ (Auto)-phagolysosome fusion             | In vitro | Mtb      | 84-221-223|
| 2062a                     | ↑ (Auto)-phagolysosome fusion             | In vitro | Mtb      | 85        |
| GM-CSF                    | ↑ Phagocytosis                            | In vitro | Mtb, Mav | 86-92     |
| Resveratrol               | ↑ (Auto)-phagolysosome fusion             | In vitro | Mtb      | 70        |
| SRT1720                   | ↑ (auto)-phagolysosome fusion             | In vitro | Mtb      | 70        |
| Celecoxib                 | ↑ Phagocytosis                            | In vivo, (R)CT | Mtb | 187     |
| Statins                   | ↑ Phagosome maturation                    | In vitro | Mtb      | 181,184-186|
| Autophagy                 |                                | In vitro | Mtb      | 26,27     |
| Imatinib                  | ↑ Autophagy                               | In vitro | Mtb      | 26,27     |
| Vitamin-D                 | ↑ Autophagy                               | In vitro, (R)CT | Mtb | 40-47,51,52|

(Continues)
| Compound                  | Biological activity | Model                   | Pathogen | Reference | Compound                  | Biological activity | Model | Pathogen | Reference |
|--------------------------|---------------------|-------------------------|----------|-----------|--------------------------|---------------------|-------|----------|-----------|
| PBA                      | ↑ Autophagy         | In vitro, (R)CT         | Mtb      | 49-53     | Doramapimod              | ↓ Necrosis          | In vitro | Mtb      | 157       |
| Vitamin-A (± Zn²⁺)       | ↑ Autophagy         | In vitro, in vivo, (R)CT| Mtb      | 55-62     | Alisporivir              | ↓ Necrosis          | In vivo  | Mm       | 36.3      |
| MirNA-27a antagomir      | ↑ Autophagy         | In vivo                 | Mtb      | 66        | Desipramine              | ↓ Necrosis          | In vivo  | Mm       | 36.3      |
| Everolimus               | ↑ Autophagy         | In vitro, (R)CT         | Mtb      | 68        | Cilostazol               | ↓ TNF-α             | In vivo  | Mtb      | 36.4,165  |
| Ibrutinib                | ↑ Autophagy         | In vitro, ex vivo       | Mtb      | 69        | Sildenafil               | ↓ TNF-α             | In vitro | Mtb      | 36.4,165  |
| Metformin⁴               | ↑ Autophagy, ↓ Mitochondrial dysfunction | In vitro, in vivo, (R)CT     | Mtb      | 71-77     | Ferrostatin 1            | ↑ Apoptosis         | Ex vivo, | Mtb      | 171       |
| Gefitinib⁴               | ↑ Autophagy         | In vitro, in vivo       | Mtb      | 78        | D-1MT³                   | ↑ Apoptosis         | In vitro | Mtb      | 129       |
| Bazedoxifene²            | ↑ Autophagy         | In vitro                | Mtb      | 79        | ATP administration³      | ↑ Apoptosis         | In vitro | Mtb, Mav | 176,177   |
| Loperamide               | ↑ Autophagy         | In vitro, ex vivo       | Mtb      | 80        | Cabrohydride and lipids  |                    |        |          |           |
| Bedaquiline²             | ↑ Autophagy         | In vitro, in vivo, (R)CT| Mtb      | 84,221-223 | 2-DG                    | ↓ Glycolysis        | In vitro | Mtb      | 174       |
| 206²                    | ↑ Autophagy         | In vitro, in vivo       | Mtb      | FX11      | ATP administration³      | ↑ Iron chelation    | In vitro | Mtb, Mav | 176,177   |
| Resveratrol³             | ↑ Autophagy         | In vitro                | Mtb      | 70        | Clemsgine                | ↑ Immune response?  | In vivo  | Mm       |           |
| SR1720⁹                 | ↑ Autophagy         | In vitro, in vivo       | Mtb      | 70        | Ezetimibe                | ↓ Lipid droplet accumulation | In vitro | Mtb      | 179       |
| miRNA-125 inh.²          | ↑ Autophagy         | In vitro                | Mtb      | 19        | M1                      | ↓ Mitochondrial dysfunction | In vitro | Mtb      | 180       |
| miRNA-23a-5p inh.³       | ↑ Autophagy         | In vitro                | Mtb      | 20        | Statins³                | ↓ Membranal cholesterol incorporation | In vitro, | Mtb      | 181,184-186 |
| Statins³                | ↑ Autophagy         | In vitro, in vivo, (R)CT| Mtb      | 181,184-186 | Statins³                | ↑ Membranal cholesterol incorporation | In vitro, | Mtb      | 181,184-186 |
| Intracellular killing mechanisms |                     |                        |          |           | Eicosanoids              |                     |        |          |           |
| CD157                    | ↑ Reactive oxygen species | In vitro             | Mtb      | 95-97     | PGE2 and/or Zileuton     | ↑ IL-1β/prostaglandin signaling | In vivo  | Mtb      | 189,190   |
| N-acetyl-cysteine        | ↓ Reactive oxygen species | In vitro, in vivo, (R)CT| Mtb      | 99-101    | Celecoxib²              | ↓ IL-1β/prostaglandin signaling | In vivo, | Mtb      | 187       |
| L-arginine               | ↑ Reactive nitrogen species | (R)CT                | Mtb      | 107-109   | LTB4⁴                   | ↑ IL-1β/prostaglandin signaling | In vivo  | Mtb      | 187       |
| Bazedoxifene²            | ↑ Reactive oxygen species | In vitro              | Mtb      | 79        | Ibuprofen               | ↓ IL-1β/prostaglandin signaling | In vivo, | Mtb      | 192,193   |
| Metformin³               | ↑ Reactive oxygen species | In vitro, in vivo, (R)CT| Mtb      | 71-77     | Aspirin                 | ↓ IL-1β/prostaglandin signaling | In vivo, | Mtb      | 193-198   |
| Celecoxib³               | ↑ Reactive oxygen species | In vivo, (R)CT          | Mtb      | 187       | Granuloma: Formation, angiogenesis and hypoxia |                      |        |          |           |

(Continues)
| Compound         | Biological activity                      | Model              | Pathogen | Reference | Compound         | Biological activity                      | Model              | Pathogen | Reference |
|------------------|------------------------------------------|--------------------|----------|-----------|------------------|------------------------------------------|--------------------|----------|-----------|
| Epigenetic regulation |                                          |                    |          |           | Cipemastat       | ↓ MMP/ECM degradation                    | In vivo            | Mtb      | 208       |
| TMP195           | ↑ Host-protective epigenetics             | In vitro, in vivo  | Mtb, Mm  | 115       | TMP195           | ↑ Host-protective epigenetics             | In vitro, in vivo  | Mtb      | 25        |
| TMP269           | ↑ Host-protective epigenetics             | In vitro, in vivo  | Mtb, Mm  | 115       | Sb-3ct           | ↓ MMP/ECM degradation                    | In vivo            | Mtb      | 212, 213  |
| Trichostatin A   | ↑ Host-protective epigenetics             | In vitro, in vivo  | Mtb, Mm  | 115       | AB0046           | ↓ MMP/ECM degradation                    | In vivo            | Mtb      | 36, 6     |
| Resveratrol      | ↑ Host-protective epigenetics             | In vitro           | Mtb      | 70        | Doxycycline      | ↓ MMP/ECM degradation                    | In vitro, in vivo  | Mtb      | 230, 234  |
| SRT1720          | ↑ Host-protective epigenetics             | In vitro, in vivo  | Mtb      | 70        | Marimastat       | ↓ MMP/ECM degradation                    | In vitro, in vivo  | Mtb      | 203, 205  |
| Valproic acid    | ↑ Host-protective epigenetics             | In vitro           | Mtb      | 117       | Batimastat       | ↓ MMP/ECM degradation                    | In vivo            | Mtb      | 205       |
| SAHA             | ↑ Host-protective epigenetics             | In vitro           | Mtb      | 117       | MMP-9 inhib.     | ↓ MMP/ECM degradation                    | In vivo            | Mtb      | 205       |
|                  |                                          |                    |          |           | Bevacizumab      | ↓ Angiogenesis                           | In vivo            | Mtb      | 217       |
|                  |                                          |                    |          |           | SU5416           | ↓ Angiogenesis                           | In vivo            | Mm       | 218       |
|                  |                                          |                    |          |           | Pazopanib        | ↓ Angiogenesis                           | In vivo            | Mm       | 218       |
|                  |                                          |                    |          |           | AKB-9785         | ↓ Angiogenesis                           | In vivo            | Mm       | 219       |

Abbreviations: (R)CT, (randomized) clinical trial; 2-DG, 2-deoxy-D-glucose; ATP, adenosine triphosphatases; CR, case report; GM-CSF, granulocyte-macrophage colony-stimulating factor; HMBPP, (E)-4-hydroxy-3-methyl-but-2-enyl pyrophosphate; IFN-γ, interferon-γ; IL, interleukin; inhib., inhibitor; LTB4, leukotriene-B4; Mav, Mycobacterium avium; Mm, Mycobacterium marinum; MMP, matrix metalloproteinase; Mtb, Mycobacterium tuberculosis; PBA, phenylbutyrate; PBMCs, peripheral blood mononuclear cells; PRR, pathogen recognition receptor; SAHA, suberoylanilide hydroxamic acid; TNF-α, tumor necrosis factor-α.

Compounds targeting distinct host intracellular pathways are categorized under multiple sections.

[Correction added on 07 March 2021, after first online publication: the Table 1 has been updated in this version.]
Mtb, positioning PPRs as potential HDT targets to combat mycobacterial infections. Furthermore, also downstream PRR signaling might be modulated by HDT. TLR2-dependent expression of miRNA-125 hampered autophagy in murine macrophages. TLR2-MyD88 signaling in Mtb-infected murine macrophages was also repressed by upregulation of miRNA-23a-5p, restricting Mtb infection–induced autophagy and thus increasing intracellular Mtb survival. Inhibition of miRNA-125 or miRNA-23a both reduced Mtb survival, identifying miRNA-125 and miRNA-23a as potential targets for HDTs.

After phagocytosis, mycobacteria become localized in phagosomes that are initially non-degradative, but slowly mature into increasingly hostile organelles. This so-called phagosome maturation hinges upon fusion with lysosomes that contain antimicrobial peptides and induce intravesicular acidification enhancing lysosomal enzyme activity. While initially thought to be simply transport vehicles, phagosomes have appeared to be highly dynamic structures that are regulated by several membrane markers, such as PI3P, acidifying proton adenosine triphosphatases (ATPases), and Rab-GTPases. As GTPases are also involved in autophagy induction, these enzymes could be interesting targets for HDT, but as of yet have not been investigated in this context. To prevent (auto)phagosome maturation, Mtb secretes proteins such as SapM and PknG, which inhibit PI3P-phosphorylation, dissociation of early endosomal protein Rab5 and acquisition of late endosomal protein Rab7. In addition, Mtb prevents recruitment of the proton pumping enzyme vacuolar-type H⁺-ATPase (v-ATPase) by phagosomes, thus further arresting phagosome acidification. Several receptor tyrosine kinases (RTKs) that are activated upon internalization of Mtb and NTM are involved in both bacterial uptake and intracellular trafficking, and could be exploited as targets for HDT. Abelson tyrosine kinase (Abi), involved in bacterial uptake by regulating cytoskeletal dynamics in host cells, can be chemically inhibited by imatinib, and indeed, imatinib treatment impaired internalization of Mtb by human macrophages. Furthermore, Abi also modulates the expression of v-ATPase, and inhibiting RTKs with imatinib induced expression of several v-ATPase pump-subunits and their colocalization with Mtb-containing phagosomes, promoting phagosomal acidification and enhancing bacterial killing in human macrophages. In line with this, imatinib treatment of mice infected with Mtb or Mycobacterium marinum (Mm) decreased mycobacterial load and combining imatinib with first-line anti-TB drug rifampicin synergistically reduced mycobacterial load in mice and in a murine macrophage-like cell line. The potential of inhibiting host tyrosine kinases to impair intracellular mycobacterial survival is further highlighted with AZD0530 treatment, a Src-inhibitor, that lowered disease burden in Mtb-infected guinea pigs by promoting phagosomal acidification. Moreover, Korbee et al showed that inhibiting RTK signaling with the repurposed drugs AT9283, ENMD-2076 and dovitinib significantly reduced intracellular Mtb in primary human macrophages. Being repurposed, these compounds are already FDA-approved or in phase II and III clinical trials, thus accelerating potential clinical application as adjunct therapy in treating (MDR)-TB and treatment of refractory NTM infections.

Formation and subsequent acidification of phagolysosomes is also inhibited by Mtb-secreted protein 1-tuberculosinadenosine antacid (1-TbAd). Accumulation of 1-TbAd in acidic intracellular compartments resulted in swelling and ultimately bursting of phagosomes, permitting mycobacterial escape into the cytosol. To further impair phagosome integrity, Mtb permeabilizes phagosomal membranes using the bacterial ESX-1 secretion system (ie, ESAT-6), which leads to leakage of phagosomal cargo into the cytosol, allowing phagosomal escape of mycobacteria. Although the cytosol contains an abundance of nutrients to support bacterial growth, translocation into the cytosol also activates DNA- and RNA-sensing pathways via intracellular recognition of PAMPs and danger-associated molecular patterns (DAMPs) to induce anti-mycobacterial host effector mechanisms. Retinoic acid-inducible gene I (RIG-I)-like receptors are cytosolic PRRs recognizing single- and double-stranded RNA and upon ligation induce the type-I IFN pathway, among others. Nucleotide-binding oligomerization domain (NOD)-like receptors are intracellular sensors for several DAMPs and PAMPs, including bacterial RNA, that can induce both type-I IFN and IL-1 responses. Enhancing expression levels of RIG-I-like receptors using nitazoxanide treatment during mycobacterial infection increased IFN-β levels and concomitantly reduced mycobacterial loads in an in vitro TB model, but did not show efficacy in TB patients, possibly due to negligible concentrations at the site of infection.

2.2 Autophagy

Autophagy is a mechanism mediating self-maintenance and cellular homeostasis and is induced under stress such as hypoxia, starvation but also microbial infection. Autophagy is crucial during Mtb and NTM infections and inhibition of autophagy using azithromycin increases susceptibility of cystic fibrosis patients to NTM infection. Autophagy is initiated by formation of a double-membraned phagophore that, under stringent control of ubiquitin-like protein conjugation systems, expands around the intracytoplasmic cargo to form autophagosomes, which ultimately fuse with lysosomes to mediate degradation. Two autophagic pathways are important for mycobacterial degradation: LC3-associated phagocytosis (LAP) and the STING-dependent cytosolic pathway. LAP is initiated by downstream signaling of numerous receptors, including TLRs, after which the phagosome becomes decorated with PI3P produced by the PI3KC3 complex, that includes Beclin-1 and Rubicon. PI3P and Rubicon are required for the generation of reactive oxygen species (ROS) and conjugation of lipidated LC3-II to the membrane to enhance phagosomal maturation. The STING-dependent pathway is triggered by mycobacterial DNA released into the cytosol through the bacterial ESX-1 system. When mycobacterial DNA is sensed by a STING-dependent DNA sensor, cytosolic Mtb is ubiquitinated by the ubiquitin-ligating (E3) ligase, bound to autophagic receptors including p62/sequestosome 1, NDP52 protein and TBK1, and subsequently delivered to autophagosomes by engagement of membrane-associated LC3.
Numerous drugs have been identified that promote autophagy by targeting different components of the autophagic pathways. Beclin-1 is induced by human antimicrobial peptide (AMP) LL-37, also known as cathelicidin. Cathelicidin is able to suppress Mtb growth and can be induced by pathogens after TLR2/TLR1 ligation, and also by vitamin-D. In vitro experiments identified calcitriol, the bioactive metabolite of vitamin-D, to exert antimicrobial activity by mediating intracellular killing of Mtb through cathelicidin. Calcitriol has also been linked to nitric oxide (NO) production and suppression of matrix metalloproteases (MMPs) which may further protect the host from TB immunopathology. The efficacy of vitamin-D as HDT during TB disease has been investigated in multiple randomized controlled trials (RCTs). Vitamin-D administration corrected any vitamin-D deficiencies and was safe in use but did not show consistent beneficial outcomes during mycobacterial infections in meta-analyses. Acceleration of Mtb clearance from sputum was mainly observed in MDR-TB cases or patients with a specific genotype, such as polymorphisms in the vitamin-D receptor gene. Furthermore, low levels of vitamin-D have been linked to a higher susceptibility to develop TB disease. Some studies combined vitamin-D therapy with phenylbutyrate (PBA), which stimulates cathelicidin-induced autophagy and also inhibits bacterial growth directly. Combining vitamin-D and PBA treatment further increased expression of cathelicidin in healthy volunteers, but the augmented expression level was constrained to a defined dose range of PBA. The narrow therapeutic window of PBA might clarify why certain RCTs failed to detect accelerated sputum-smear conversion by co-administering vitamin-D and PBA and only showed accelerated sputum-smear conversion at week 4 following combined treatment, but not at week 8 in vitamin-D-deficient patients. Due to these inconsistencies, progression of vitamin-D as potential HDT in TB treatment regimens has not been successful.

Vitamin-A deficiency has also been correlated with an increased risk to develop TB disease. STING-dependent autophagy can be targeted by the active metabolite of vitamin-A, that is, all-trans retinoic acid (ATRA), which promotes TBK1-mediated enhancement of autophagy which reduces Mtb survival in human macrophages. ATRA is also known to increase CD1d receptor expression on innate immune cells, and treatment with non-mycobacterial CD1d ligand α-galactosylceramide (α-GalCer) reduced mycobacterial load and improved survival of mice with TB. and while α-GalCer combined with ATRA and vitamin-D did not clear the infection in mice, it improved containment of the infection. In patients, vitamin-A supplementation combined with Zn or vitamin-D gave inconsistent results. Thus, although vitamin-A reduced Mtb loads in vitro and in vivo, evidence for its efficacy in patients is inconsistent. An additional regulator of the selective STING-dependent autophagy pathway is DNA-damage regulated autophagy-modulator protein 1 (DRAM1). DRAM1 was found to trigger autophagy in both Mtb-infected human macrophages and Mm-infected zebrafish larvae, whereas DRAM1-deficiency resulted in host-detrimental cell death, underscoring DRAM1 as an interesting target for HDT.

In addition to Beclin-1 and TBK1, other components of the autophagic pathways have also been targeted to promote mycobacterial clearance. Ca²⁺ signaling is pivotal in inducing autophagy by activating the Ca²⁺/calmodulin-dependent serine/threonine-kinase (CaMKK2)/ULK1 complex. CaMKK2-mediated autophagy and killing of intracellular Mtb requires Ca²⁺ transporter CACNA2D3 which is, however, suppressed by Mtb-induced miRNA27a. Intracellular survival of Mtb could be impaired by inhibiting miRNA-27, providing a new HDT target.

Another important negative regulator of autophagy is the PI3K-Akt-mTOR signaling pathway, which is robustly activated by Mtb to facilitate its intracellular survival. Everolimus, an improved analog of mTOR inhibitor rapamycin, was able to reduce Mtb burden in a human granuloma model and these effects were additive to first-line TB drugs, possibly by HDT activity and/or by inhibiting mycobacterial growth directly. Inhibition of protein-kinase C-beta (PKC-B), another important regulator of the PI3K-Akt-mTOR pathway, by ibrutinib also enhanced autophagy and restricted intracellular growth of Mtb in macrophages and mice in the spleen, although not in the lungs. Alleviating the Mtb-mediated suppression of sirtuin-1, a class-III histone deacetylase that also modulates autophagy via 5AMP-activated protein-kinase (AMPK), using resveratrol restricted intracellular Mtb growth by stimulating autophagy and phagosome-lysosome fusion. Metformin, a well-established stimulator of AMPK-mediated inhibition of mTOR signaling, is widely used for the treatment of type-2 diabetes, but also induces ROS production, phagosome maturation, and autophagy in vitro and prevents mitochondrial membrane depolarization. In non-diabetic healthy volunteers, metformin treatment downregulated genes involved in Mtb-mediated modulation of autophagy, as well as type-I IFN signaling, while upregulating genes involved in phagocytosis and ROS production. Several clinical trials have shown that metformin treatment reduces the risk of latent TB reactivation and TB mortality, and in patients with cavitory TB, improves sputum culture conversion.

Like metformin, repurposing of drugs that are clinically approved in the context of other diseases has been shown to enhance autophagy and to reduce intracellular bacterial growth, suggesting these drugs may be considered as HDT candidates. The anti-cancer drug gefitinib, an inhibitor of epidermal growth factor receptor (EGFR), promotes intracellular Mtb killing by alleviating the STAT3-dependent repression of effective immune responses in Mtb-infected mice and by enhancing lysosomal biogenesis and targeting of mycobacteria to lysosomes in Mtb-infected macrophages. Gefitinib also induced autophagy, but since no specific targeting of mycobacteria to the autophagic pathway was observed, this activity has not been formally linked to restricting intracellular Mtb survival. Bazedoxifene, a selective estrogen receptor modulator (SERM) used for breast cancer treatment, was also shown to inhibit intracellular Mtb growth in macrophages through enhanced ROS-dependent autophagy and to inhibit Mtb growth in liquid culture. Furthermore, one study showed that loperamide, an anti-diarrheal drug, promoted autophagy as indicated by p62 degradation and decreased mycobacterial burden in vitro and ex vivo in murine macrophages.
Mtb not only inhibits the initiation of autophagy, but also fusion of autophagosomes with lysosomes via protein P2-PGRS47. Furthermore, the Mtb secretion-factor SapM inhibits Rab7-recruitment to prevent autophagosomes-lyosome fusion. Mtb-expressed mannosylated lipoparabinomannan (ManLAM) also inhibits maturation of autophagosomes, by blocking LC3-translocation to autophagosome membranes. Releasing such blockades in autophagosome-lysosome fusion could represent potential HDT strategies. Bedaquiline, a novel antibiotic now in use for MDR-TB, has also been shown to induce phagosome-lysosome fusion and autophagy via activation of TFEB, possibly contributing to its successful application as a new TB drug. In line with this, a small molecule called 2062 improved autophagy and lysosomal pathway activity via activation of TFEB when administered with suboptimal doses of rifampicin.

Although autophagy-targeting HDTs have been investigated mainly in the context of Mtb infections, several case reports have been published for (disseminated) Mav infections in patients who received granulocyte-macrophage colony-stimulating factor (GM-CSF) or IFN-γ. GM-CSF treatment during Mtb infection reduced bacterial burden by promoting phagosome-lysosome fusion and increased expression of TNF-α, IFN-γ, and inducible nitric oxide synthase (iNOS). GM-CSF treatment during Mav infection increased phagocytosis and impaired bacterial growth in vitro in human macrophages and in Mav-infected patients with or without HIV infection (partially) improved clinical outcome. Thus, autophagy likely plays an important role also in NTM immunity, and could represent an attractive target for HDT in severe NTM infections.

2.3 | Intracellular killing mechanisms: reactive oxygen and nitrogen species

To eliminate mycobacteria during infection, host cells trigger the production of reactive oxygen species (ROS) and reactive nitrogen species (RNS), via NADPH oxidase 2 (NOX2) and inducible nitric oxide synthase 2 (iNOS), respectively. iNOS catalyzes production of nitric oxide (NO) by converting L-arginine into L-citrulline, which is subsequently converted into RNS. Once expressed, both ROS and RNS interact with the phagosome to destroy bacterial components. Mycobacterium-induced ROS production occurs via the TLR2-MyD88 signaling axis and impairments in this pathway increase susceptibility to Mtb infection. Recently, TLR2-dependent ROS production and bactericidal activity was found to be impaired in CD157-deficient murine macrophages which could be rescued by administration of soluble CD157. Moreover, expression levels of CD157, an enzyme important for leukocyte migration and involved in nicotinamide-adenine-dinucleotide (NAD+) metabolism, are elevated in patients with active TB compared to LTBI and lowered when patients are treated with TB chemotherapy, indicating an important role of CD157 in host immunity, biomarker profiling and also providing a potential HDT.

Although ROS production is important for host resistance against mycobacterial infection, modulating ROS as HDT strategy requires careful monitoring as excess ROS leads to oxidative stress and concomitant necrosis. Corroborating this view, reducing ROS accumulation in Mtb-infected macrophages with ROS scavenger N-acetyl-cysteine in fact restricted Mtb replication and restored macrophage cell viability in a guinea pig Mtb infection model. N-acetyl-cysteine administration was also shown to be efficacious. Moreover, N-acetyl-cysteine was found to be safe in a cohort of TB-HIV co-infected individuals, although its impact on culture conversion remains to be determined. Nevertheless, ROS production is important for the bactericidal activity of macrophages and the critical balance in ROS production and its regulation is important in restricting intracellular mycobacterial growth without harming the host.

Multiple studies in mice and humans have shown antimicrobial effects of NO, but the exact underlying mechanisms remain unclear. Macrophages from LTBI patients were shown to control Mtb growth via NO production, and human macrophages required iNOS for intracellular killing of Mtb. Moreover, compared to wild-type murine macrophages, protein-kinase R (PKR)-deficient macrophages induced higher levels of iNOS during Mtb infection, and PKR-deficient mice had lower Mtb loads and less severe lung pathology compared to infected wildtype mice, highlighting the potential of PKR as HDT target. Despite its importance as substrate for NO production, supplementing L-arginine did not consistently improve clinical outcomes such as cure rate or (sputum) smear conversion in several clinical trials.

Several Mtb-associated proteins have been identified that protect Mtb from RNS, but Mav naturally tolerates intracellular NO levels and may even benefit from host NO. Mice that cannot produce NO were more resistant to Mav infections, while being more prone to Mtb infections. In agreement with this, compared to wildtype mice, NOS2-deficient mice showed higher IFN-γ responses during Mav infection and increased accumulation of especially CD4+ T-cells. Enhancing NO production can thus be beneficial in combatting mycobacterial infections such as Mtb, but not Mav.

2.4 | Epigenetic regulation

Macrophage polarization is an important mechanism of the immune system to respond adequately to the plethora of pathogens, which is partly mediated by epigenetic regulation of gene expression using histone acetylation. The level of histone acetylation is regulated by the balanced activity of histone acetyltransferases (HATs) and histone deacetylases (HDACs). HDACs are divided into four classes, three of which are Zn2+-dependent (class I, IIa/IIb and IV), while class-III is NAD+-dependent. Mtb infection actively modulates the acetylation status of host histones by (a) suppressing expression of class-II HDACs (ie, HDAC 3, 5, 7, and 10) in macrophages, with anti-inflammatory M2 macrophages being more affected than pro-inflammatory M1 macrophages, (b) inhibiting the expression
of class-III HDAC sirtuin-1 both in vitro and in human tissues from TB patients, and (c) upregulating expression of sirtuin-2, another class-III HDAC that regulates cell cycle and metabolism. Type Ia-specific HDAC inhibitors (HDACi) TMP195 or TMP269 reduced bacterial loads in M2, but not M1 macrophages, while broad-spectrum HDACi trichostatin A reduced bacterial loads in both M1 and M2 macrophages. Interestingly, combining HDACi with AKT1 kinase inhibitor H-89 resulted in cumulative reduction in bacterial loads. Importantly, in a Mm zebrafish infection model, both class-IIa and pan-HDAC inhibition reduced bacterial loads, confirming the in vivo potential of HDAC inhibition as HDT to treat TB. Sirtuin-1, a class-III HDAC important during (viral) infections, regulates stress responses and cellular metabolism. Resveratrol or SRT1720, a natural and synthetic activator of sirtuin-1, enhanced clearance of drug-sensitive and drug-resistant Mtb. Both compounds stimulate autophagy and phagolysosome fusion in THP-1 cells, which likely accounts for the enhanced bacterial killing, while reducing pathology in a TB mouse model, possibly by inhibiting expression of IL-1β, IL-6, MCP-1, and TNF-α.

The Mtb genome encodes Rv1151c, a sirtuin-like NAD-dependent deacetylase, allowing Mtb to produce acetyl coenzyme A (acetyl-CoA) synthetase, a critical enzyme in energy metabolism of both host cells and bacteria. Targeting this pathway using HDACi valproic acid directly inhibited bacterial growth, likely by inhibiting acetyl-CoA production by Mtb itself, while co-treatment of valproic acid and rifampicin/isoniazid therapy resulted in cumulative effects. By contrast, FDA-approved HDACi suberoylanilide hydroxamic acid (SAHA) had no direct effect on Mtb growth, but it reduced mycobacterial growth via host-directed mechanisms and synergized with rifampicin/isoniazid therapy. As Rv1151c is well conserved across different mycobacterial species including Mav, the above therapies may also be efficacious against NTM.

3 | HDT MODULATING ADAPTIVE IMMUNE RESPONSES

3.1 | Antigen presentation and priming

Upon phagocytosis, pathogens are processed and degraded, such that pathogen-derived peptides can be loaded and presented in MHC-class I and II molecules to initiate adaptive T-cell responses. One strategy of mycobacteria to evade host adaptive immune responses is to impair presentation of mycobacterial peptides by evading phagosomal degradation. Improving mycobacterial degradation by promoting phagosomal maturation and/or autophagy induction as discussed above likely enhances both antigen presentation and concomitant adaptive immunity. Another strategy of mycobacteria to evade host adaptive immune responses is to predominantly infect macrophages instead of dendritic cells, the former requiring stronger activation before being able to efficiently process and present antigens for priming naïve T-cells. Macrophage activation is required to induce expression of CIITA, a major positive regulator of MHC-class II. By actively engaging TLR2 rather than other TLRs, Mtb (and to a lesser extent M smegmatis) minimizes upregulation of CIITA and concomitant MHC-class II expression. In addition, TLR2 (among all TLRs) most potently induces an innate (IL-6) response, leading to upregulation of suppressor-of-cytokine-signaling-1 (SOCS1) that in turn inhibits signal-transducer-and-activator-of-transcription 1 (STAT1) phosphorylation and antigen presentation, further impairing the adaptive host immune response. MiR106b, which degrades mRNA encoding cathepsin S, a protein that modulates MHC-class II molecules to allow peptide loading, is significantly upregulated during Mtb infection. Inhibition of miR106b using miRIDIAN hairpin inhibitors upregulated expression of both cathepsin S and HLA-DR and enhanced subsequent CD4 T-cell proliferation. Alternatively, inhibition of sirtuin-2 activity in macrophages using AGK2 modulated gene expression-promoted antigen presentation. AGK2 treatment of mice resulted in upregulation of MHC-class II expression but also of co-stimulatory molecules and markers of activation, leading to enhanced priming of T-cells and improved Mtb killing.

Since Mtb limits activation of antigen-presenting cells (APCs), which precludes the host from mounting an effective adaptive immune response, proper activation of APCs could be an interesting HDT. A possible strategy for HDT could be administration of G1-4A, a polysaccharide from Tinospora cordifolia that presumably signals via TLR4, or TLR4 ligand LP5 combined with a CD40 agonistic antibody. Both treatments induced vast cytokine production (IFN-γ/IL-12, TNF-α, IL-6) and upregulation of co-stimulatory molecules by dendritic cells in vitro. Furthermore, both treatments reduced bacterial loads in murine TB infection models which was, at least in part, T-cell-mediated. However, systemic administration of TLR ligands is known to cause significant side effects, and may only be applicable via local administration. Bergenin, a phytochemical extracted from tender leaves, enhanced macrophage activation, as evidenced by enhanced CD11b expression as well as augmented NO, TNF-α, and IL-12 production, through activating the MAPK/ERK pathway. The resulting increased IL-12 production induced a robust Th1 response with concomitant IFN-γ production by T-cells. Bergenin therapy reduced bacterial loads as well as lung pathology in a murine TB infection model. Of note, vaccination could also be an interesting HDT approach to activate APCs or reprogram an effective adaptive immune response. This, however, falls outside the scope of this review and is excellently reviewed elsewhere.

Due to the chronic immune stimulation during persisting mycobacterial infections, including LTBI, T-cells and APCs upregulate inhibitory receptors such as PD-1/PD-L1, which can impair T-cell effector functions, and may be interesting targets for HDT. Expression of exhaustion-associated markers by T-cells during active disease, however, is rather ambiguous: Despite successes in anti-cancer therapies by inhibiting immune checkpoint molecules with anti-PD-1/PD-L1 antibodies, PD1/PDL1-directed experimental therapies in vitro and in vivo TB models resulted in impaired intracellular control of Mtb and TB exacerbation rather than improved resolution, suggesting PD-1 may be a T-cell activation rather than exhaustion marker during TB. Moreover, reports of LTBI-reactivation in cancer
patients treated with anti-PD-1/PD-L1 warrant a cautionary note against this therapy in TB.

Indoleamine 2,3-dioxygenase (IDO) expression is actively induced by mycobacteria in animal (macaques and mice) models of acute TB, but not LTBI, and IDO levels correlated with bacterial burden. IDO catabolizes tryptophan into kynurenine, which in turn suppresses IFN-γ production by CD4 T-cells, a cytokine pivotal in the anti-TB response, identifying IDO as potential target for HDT. In vivo inhibition of IDO activity using D-1MT one week after mycobacterial infection enhanced T-cell proliferation and differentiation in effector and memory cells while apoptosis was enhanced. Furthermore, D-1MT treatment improved penetration of T-cells into granulomas, likely allowing protective T-cell-mediated granuloma reorganization, and reduced bacterial loads and lung pathology.

3.2 | Skewing of T-cells

Th1-responses, characterized by high IFN-γ secretion, are crucial in effective anti-Mtb immune responses. Nevertheless, Mav and Mtb reduce cellular responses to IFN-γ and deficiencies in the IL-12/IL-23/IFN-γ-axis increase susceptibility to Mav infections. In several patients suffering from pulmonary TB, direct administration of IFN-γ accelerated sputum-smear conversion and improved chest radiograph. Administration of IFN-γ also reduced Mav growth in murine macrophages and improved clinical outcome (i.e., decreased respiratory symptoms and mortality) in several but not all Mav-infected individuals, suggesting potential of IFN-γ as HDT in both Mtb and Mav infections. In vivo administration of IL-12, a key cytokine that drives Th1 skewing, enhanced IFN-γ and TNF-α responses and significantly reduced bacterial burden in an acute mouse TB model. Similarly, restoring IL-24 expression in a mouse TB model enhanced Th1-responses and IFN-γ production, with concomitant improved survival and reduced bacterial loads. A large proportion of human Mtb-specific CD4 Th1-cells expresses CCR6 and co-produces IFN-γ/IL-17, often depicted as Th1* or Th1-17 cells, and being associated with LTBI suggests their importance in protection against active TB. However, IL-17 responses during TB need to be carefully regulated to prevent neutrophil-driven lung pathology, which is mediated by regulatory T-cells as well as so-called regulatory CD4 Th17-cells that co-produce IL-17 and IL-10. In case of disbalanced Th17 responses with concomitant excessive neutrophil recruitment, RAGE receptor inhibition may be an interesting HDT. RAGE receptor is up-regulated during active TB disease and after ligation with S100A8/A9 mediates neutrophil recruitment. In a TB model, mice deficient in S100A8/A9 had reduced bacterial loads, neutrophil influx and pathology compared to wildtype. Moreover, inhibition of the RAGE receptor using FPS-ZM1 improved outcome comparably as S100A8/A9-deficiency.

Th2-responses have been associated with active cavitary TB disease or TB treatment failure and administration of IL-4, a hallmark Th2-cytokine, impaired mycobacterial control by human macrophages and enhanced the proportion of regulatory T-cells in vitro. Blocking IL-4 completely alleviated these effects and improved bacterial control, suggesting Th skewing could be an interesting target for HDT.

Alternatively, administration of IL-2, which stimulates T-cell proliferation while inhibiting T-cell anergy, in patients infected with drug-resistant Mtb has been investigated in five RCTs and compared in a meta-analysis. While CD4 T-cell numbers increased and time to culture conversion improved, radiographic changes were not observed compared to standard chemotherapy. In mice infected with Mav, IL-2 therapy resulted in decreased bacterial burden, whereas mixed results were described in case reports. The limited effect of IL-2 therapy may be due to immune suppression caused by expansion of regulatory T-cells and myeloid-derived suppressor cells (MDSC), both expressing elevated levels of the high affinity IL-2 receptor, as depletion of these suppressor cells improved outcome in a mouse TB model. Combining IL-2 therapy with mycobacterial phosphoantigens (E)-4-hydroxy-3-methyl-but-2-enyl pyrophosphate (HMBPP) in non-human primates induced significant expansion of Vγ2Vδ2 T-cells that migrated to the lungs, evoking a Th1-response that significantly reduced mycobacterial burden as well as lung pathology. Rather than systemic administration of cytokines, which frequently results in systemic side effects, ex vivo stimulation of autologous peripheral blood mononuclear cells (PBMCs) with a cocktail of IFN-γ, IL-2, IL-1α, and anti-CD3 before reinfusion yielded positive results with minimal side effects in a case report with MDR-TB. This, however, requires further clinical investigation.

4 | (PROGRAMMED) CELL DEATH

Several types of cell death can follow mycobacterial infection of macrophages: apoptosis, necrosis, and ferroptosis. During apoptosis, bacteria remain encapsulated, which facilitates bacterial clearance; however, pathogenic mycobacteria have developed strategies to limit apoptosis. Activation of transcriptional regulator peroxisome proliferator-activated receptor gamma (PPARγ) by ManLAM, stimulating mannose receptors, upregulated (pro-host-cell survival) Mcl-1 and repressed (pro-apoptotic) Bax without Bak and improved host-cell survival. In agreement with the PPARγ-dependent inhibition of host-cell apoptosis and concomitant anti-mycobacterial immunity, direct pharmacological inhibition of Mcl-1 resulted in reduced intracellular Mtb growth in human macrophages.

Besides inhibiting apoptosis, virulent Mtb stimulates host-cell necrosis, which allows infection to disseminate to neighboring cells. Mtb can induce necrosis via the virulence factor tuberculosis necrotizing toxin (TNT), which is secreted into the cytosol where its NAD+-glycohydrolase activity depletes the host cell from NAD+, leading to permeabilization of mitochondrial membranes, decreasing ATP-production and activating necrosis. Nicotinamide-based HDT alleviated necrosis-induced host-cell cytotoxicity in Mtb-infected cells by replenishing NAD+. Mtb can furthermore induce necrosis mediated by
mitochondrial membrane permeability transition via p38-MAPK phosphorylation, which can be inhibited by corticosteroids dexamethasone and doramapimod.\textsuperscript{157} In addition, corticosteroids dexamethasone and prednisolone, both well-known general immunosuppressants, have also been investigated as HDT during mycobacterial infections. With some reports of improved survival,\textsuperscript{158,159} likely by limiting secretion of pro-inflammatory cytokines, meta-analysis failed to show a significant improvement in clinical outcome after corticosteroid therapy in patients with TB.\textsuperscript{160} Interestingly, while promoting pro-inflammatory cytokine levels of TNF-\(\alpha\) by adenyate cyclase inhibitor (SQ22536) or a PKA inhibitor (H-89) has been shown to control infection by stimulating mitochondrial ROS production,\textsuperscript{161} excess TNF-\(\alpha\) leads to membrane disruption and ATP depletion via mitochondrial enzyme cyclophilin D, which together with lysosomal enzyme acid sphingomyelinase induced necrosis.\textsuperscript{162,163} Alisporivir and desipramine, two clinically approved drugs that inhibit cyclophilin D and acid sphingomyelinase, respectively, prevented TNF-\(\alpha\)-induced necrosis without compromising TNF-\(\alpha\)-induced ROS-dependent mycobacterial killing.\textsuperscript{163} Correspondingly, upregulation of cAMP levels by phosphodiesterase (PDE) inhibitors cilostazol and sildenafil decreased TNF-\(\alpha\) levels, resulting in reduced immunopathology and fastened bacterial clearance in \(Mtb\)-infected mice.\textsuperscript{164,165} Blocking TNF-\(\alpha\), which facilitates necrotizing granulomas during active TB, displayed promising results in preclinical animal models.\textsuperscript{166,167} However, blocking TNF-\(\alpha\) also leads to disease reactivation and concomitant disemination in LTBI patients and in the absence of standard TB chemotherapy exacerbated disease severity.\textsuperscript{168,170} precluding clinical application of TNF-\(\alpha\) inhibition as HDT in TB. The balance between TNF-\(\alpha\)-mediated beneficial and detrimental effects on host control of TB and likely other mycobacterial infections including NTM is thus delicate. Taken together, these data indicate that \(Mtb\)-induced host-cell necrosis favors mycobacterial survival and this can be effectively counteracted by HDT, while the double-edge sword of modulating TNF-\(\alpha\) levels currently prohibits clinical application.

Ferroptosis is a type of necrosis characterized by accumulation of free iron and toxic lipid peroxides.\textsuperscript{171} In \(Mtb\)-infected cells expression of glutathione peroxidase-4 (GPX4) is reduced, leading to failure of glutathione-dependent antioxidant defenses and cell death.\textsuperscript{172} Inhibiting ferroptosis by ferrostatin 1 reduced bacterial burden both in vitro in human macrophages and in vivo in \(Mtb\)-infected mice.\textsuperscript{171} Furthermore, ferroptosis could also be inhibited by increasing GPX4 levels with selenium, a protein involved in GPX4 catalysis,\textsuperscript{173} showing that targeting this host pathway is a potential HDT strategy.

5 | METABOLISM

5.1 | Carbohydrate and lipids

\(Mtb\) has developed numerous strategies to modulate host metabolic pathways, which are broadly divided into glycolysis, oxidative phosphorylation (OXPHOS), and lipid metabolism. Glycolysis conditions an environment favoring \(Mtb\) growth, and inhibition of glycolysis using 2-deoxy-D-glucose (2-DG) reduced \(Mtb\) viability in one study, and as a result of ATP depletion induced macrophage apoptosis.\textsuperscript{174} An important enzyme during glycolysis, lactate dehydrogenase (LDH), which converts pyruvate into lactate, is significantly upregulated during \(Mtb\) infection.\textsuperscript{175} Although the pathophysiology of LDH upregulation remains to be addressed, pharmacological inhibition of LDH using FX11 reduced bacterial load and development of necrotic lesions in granulomas in a murine TB model, suggesting a significant role of LDH in driving disease and a potential target for HDT.\textsuperscript{175} Interestingly, while ATP depletion can induce macrophage apoptosis (considered host protective), exogenous ATP activates macrophages via the P2RX\(_7/P2X\(_7\) receptor and also directly inhibits growth of mycobacteria, including \(Mtb\) and \(Mav\), due to chelation of iron.\textsuperscript{176,177} ATP treatment has already been shown to synergize with standard \(Mav\) antibiotic treatment, making ATP an interesting adjunctive HDT molecule to enhance chemo-therapeutic efficacy against mycobacterial infections.\textsuperscript{177} In addition, an FDA-approved potentiator of P2RX\(_7/P2X\(_7\), clemastine enhanced mycobacterial killing in a zebrafish model.\textsuperscript{178} This may provide a potentially attractive avenue to explore synergistic effects between ATP and clemastine treatment in future studies.

Conversion of pyruvate into acetyl coenzyme A (Ac-CoA) initiates the tricarboxylic acid (TCA) cycle which produces energy using OXPHOS. During \(Mtb\) infection, several enzymes important in the TCA cycle are downregulated and TCA cycle intermediates, such as citrate, are translocated from mitochondria into the cytosol. Typically, citrate is converted into itaconate which dampens tissue hyperinflammation by suppressing both ROS production and production of pro-inflammatory cytokines such as IL-1\(\alpha\), IL-6, and IL-12.\textsuperscript{174} In the cytosol, however, citrate is cleaved into Ac-CoA, which is either converted into arachidonic acid or into mevalonate and malonyl-CoA. This leads to synthesis of eicosanoids, cholesterol, and free fatty acids, respectively, of which the latter two are stored intracellularly in lipid droplets.\textsuperscript{174} Hypercholesterolemia results in spontaneous formation of lipid droplets in macrophages. Further accumulation of intracellular lipid droplets is actively stimulated by \(Mtb\) and enhanced by both IL-6 and TNF-\(\alpha\) signaling, while IL-17 and IFN-\(\gamma\) limit intracellular lipid accumulation.\textsuperscript{174} Lipid-loaded macrophages are impaired in killing intracellular mycobacteria (ie, \(Mtb\), \(Mav\), and BCG)\textsuperscript{180} and ultimately transform into foamy macrophages, which are associated with necrotic granulomas and tissue pathology.\textsuperscript{174} The impaired functionality of lipid-loaded macrophages involves mitochondrial dysfunction and could be restored using small molecule mitochondrial fusion promoter M1, which also restored macrophage bactericidal activity.\textsuperscript{180} In addition, ezetimibe, a cholesterol absorption inhibitor, prevented intracellular lipid accumulation and concomitantly reduced intracellular growth in \(Mtb\)-infected macrophages.\textsuperscript{179} The effects of standard antibiotic treatment improved and perhaps even synergized with ezetimibe treatment,\textsuperscript{179} and investigating the in vivo efficacy of ezetimibe as well as M1 could be promising.

Statins, currently clinically used to reduce cholesterol levels, could be interesting drugs to prevent lipid accumulation in macrophages. Comparing eight different statins, simvastatin, pravastatin and fluvastatin were most efficacious in enhancing mycobacterial
Eicosanoids

Eicosanoids are lipid mediators involved in regulating inflammatory responses and are categorized into prostaglandins (PG), leukotrienes (LT), thromboxanes, lipoxins, and hydroxy eicosatetraenoic acids, all of which are produced from arachidonic acid by a competing network of enzymes, including cyclooxygenases (COX) and lipoxygenases.\(^\text{187,188}\) During Mtb infection, the expression of eicosanoids is significantly altered, with prostaglandin-E2 (PGE2) and leukotriene-B4 (LTB4) mostly upregulated.\(^\text{187}\) Being an immune suppressor and immune stimulator, respectively, the balance between these eicosanoids is highly important in regulating immunity to clear the infection, without causing tissue pathology due to excessive inflammation. Important in this regulation are IL-1\(\beta\) and type-I IFN signaling. IL-1\(\beta\) signaling stimulates production of prostaglandin-E2, which is necessary to dampen the inflammation mediated by pro-inflammatory leukotrienes A\(_4\) and B\(_4\) (LTA\(_4\) is the precursor of LTB\(_4\)) that are induced upon type-I IFN signaling. In severe TB, the PGE2/LTA\(_4\) ratio is reduced, suggesting potential benefit of enhancing PGE2 signaling. Indeed, both increasing PGE2 levels using administration of exogenous PGE2 or reducing LTA\(_4\)/LTB\(_4\) production with zileuton improved host survival, while reducing bacterial loads and necrotic lung pathology in Mtb-infected mice.\(^\text{189}\) Moreover, combinatory therapy of zileuton with PGE2 further restricted Mtb replication.\(^\text{190}\)

A single nucleotide polymorphism in the promoter of the gene encoding LTA\(_4\)-hydrolase (rs17525495), the enzyme that converts LTA\(_4\) into LTB\(_4\), has been shown to affect expression of LTA\(_4\)-hydrolase, with homozygous individuals having a high (T/T) or low (C/C) expression.\(^\text{188,191}\) Both homozygous genotypes have poorer survival compared to heterozygous individuals, showing the delicateness of the immune balance during mycobacterial infection.\(^\text{188}\) Depending on the genotype, different treatment regimens will be required, as general immune suppression using dexamethasone favored outcome in T/T individuals, while being detrimental in C/C individuals.\(^\text{188,191}\) Suggesting the necessity of personalized HDT-based medicine targeting eicosanoid metabolism. Mice deficient in 5-lipoxygenase, an enzyme that stimulates production of LTA\(_4\) and thus LTB\(_4\) (thereby being a model for C/C individuals), were impaired in controlling mycobacterial infection due to absence of LTB\(_4\). Treatment with celecoxib, a COX inhibitor that prevents PGE2 production and thereby stimulates LTB\(_4\) production, or directly supplementing LTB\(_4\), restored mycobacterial control.\(^\text{187}\) Furthermore, COX inhibitors ibuprofen and aspirin administered as single therapy or combined with conventional TB antibiotics were shown to limit bacterial burden in Mtb-infected mice,\(^\text{192-194}\) and low-dose aspirin treatment also reduced bacterial loads in a Mm zebrafish infection model.\(^\text{195}\) Aspirin treatment of TB or TB meningitis patients improved survival,\(^\text{196,197}\) but may impair conventional treatment regimens by reducing efficacy of isoniazid,\(^\text{198}\) but not pyrazinamide.\(^\text{193}\) Both ibuprofen and aspirin are currently tested in clinical trials as adjunct therapy for treating (drug-resistant) TB.\(^\text{190}\)

### 5.2 | Eicosanoids

One hallmark of TB is the extensive formation of granulomas. Granulomas are highly heterogenous and dynamic structures which differ significantly in the level of hypoxia and available nutrients. Granuloma formation is actively initiated by Mtb to stimulate matrix metalloprotease 9 (MMP9) production. Granulomas are also induced during NTM infections, including Mav\(^\text{199,200}\) and Mm.\(^\text{201}\) During initial granuloma formation non-activated macrophages are recruited to the site of infection and serve as feeder cells for the granuloma.\(^\text{25,202}\) In addition to MMP9, upregulation of several other MMPs has been observed in lung samples from individuals infected with Mtb and other mycobacteria including Mav, which may suggest that similar mechanisms are involved.\(^\text{202-206}\) MMPs are enzymes that degrade and modulate extracellular matrix and are therefore key in the development of granulomas.\(^\text{204}\) Their expression and activity has multiple layers of regulation. Many MMPs require Zn\(^{2+}\) for their activation, potent MMPs require activation by other MMPs, and their activation is inhibited by tissue inhibitors of metalloproteinases (TIMPs). Expression of MMPs is stimulated by pro-inflammatory cytokines, including IFN-\(\gamma\), TNF-\(\alpha\), IL-12, and IL-17 and because enhanced MMP-activity is associated with extensive tissue damage during TB,\(^\text{203}\) MMPs are promising targets for HDTs.

MMP1, a collagenase that degrades collagen in the extracellular matrix, is upregulated after TLR2-ligation and due to its high potency may drive granuloma formation during TB.\(^\text{207}\) In transgenic mice expressing human MMP1, Mtb infection promoted alveolar destruction and collagen breakdown in lung granulomas, identifying MMP1 as a therapeutic target to limit immunopathology.\(^\text{207}\) MMP7, which is highly expressed in the cavitory wall and hypoxic granulomas, stimulates epithelial proliferation and promotes activity of other MMPs. Inhibition of MMP7 and MMP1 using cipemastat, a drug originally registered to prevent lung fibrosis, surprisingly increased cavitation, immunopathology and mortality in mice,\(^\text{208}\) suggesting either a protective role of MMP1 or MMP7 during TB or off-target effects of the drug. The role of MMP8 is more controversial with high interindividual variation,\(^\text{203,209,210}\) which may relate to the presence...
of neutrophils in granulomas. MMP8 is more readily detectable in HIV-associated TB, suggesting that neutrophils are recruited preferentially in settings of impaired adaptive immunity. Mice deficient in MMP9 have less granuloma formation and reduced bacterial loads, suggesting a prominent role of MMP9 in driving disease pathology. Indeed, inhibition of MMP9 expression using morpholinos reduced granuloma formation and bacterial growth in a zebrafish Mm-model. In agreement with this concept, treatment with Sb-3ct, a specific MMP2 and MMP9 inhibitor, combined with frontline TB antibiotics potentiated bacterial clearance both in vitro and in vivo in a TB meningitis mouse model. Blocking MMP9 using monoclonal antibody AB0046 did not affect bacterial burden, but the rate of relapse was reduced in a necrotic granuloma TB mouse model, by mechanisms not yet fully clarified. Using an in vitro model for extracellular matrix degradation, treatment with doxycycline, an FDA-approved antibiotic that non-selectively inhibits human MMPs, strongly abolished Mtb-induced matrix degradation. In addition, doxycycline reduced granuloma formation in a guinea pig model, likely resulting from abolishing Mtb-enhanced promoter activity of MMP1 and by directly inhibiting bacterial growth. Pan-MMP inhibitor marimastat (BB-2516), a collagen-peptidomimetic binding the active Zn²⁺ site contained in many MMPs, reduced granuloma size and bacterial burden during Mtb infection in lung tissue models. Interestingly, treatment of Mtb-infected mice with a panel of MMP inhibitors, including marimastat, as solo therapy was not effective, while all 4 small molecules enhanced in vivo potency of frontline TB inhibitors, including marimastat (BB-2516), a collagen-peptidomimetic binding the active Zn²⁺ site contained in many MMPs, reduced granuloma size and bacterial burden during Mtb infection in lung tissue models. Augmenting TIMP1 activity to inhibit activity of multiple MMPs may also be an interesting HDT target. To our knowledge, however, modulating the activity of TIMPs has not been investigated yet in the context of HDT.

Central hypoxia in granulomas may initially favor host immunity as low oxygen tension increases granulysin expression in T-cells and NK-cells, enhancing bacterial killing in an in vitro co-culture system of Mtb-specific T-cells and macrophages. However, due to poor vasculature within granulomas and hyperactive IFN-γ or possible superimposed IL-4/IL-13 released by activated T-cells, full blown central necrosis leads to cavity formation and concomitant bacterial dissemination within the host. Due to the hypoxic, acidic and nutrient-poor conditions in granulomas, mycobacterial dormancy is promoted, and while this effectively inhibits bacterial replication, eradication of mycobacteria is greatly hampered because most antibiotics only affect replicating and metabolically active bacteria. Furthermore, poor vascularization hampers drug delivery in granulomas, which is further impaired due to fibrosis and scarring of lung tissue caused by the disease. Trehalose dimycolate, a mycolic acid expressed on mycobacterial cell walls, directly induces vascular endothelial growth factor (VEGF) expression in host cells to stimulate angiogenesis. Although angiogenesis could potentially increase host-cell viability, the net effect likely favors bacterial replication and dissemination. Blocking angiogenesis may therefore be an interesting HDT. Indeed, inhibition of VEGF using FDA-approved bevacizumab in Mtb-infected rabbits, reduced the total number of vessels but improved both structurally and functionally the remaining vessels, leading to enhanced drug targeting to granulomatous lesions and diminished hypoxia. Corroborating these findings, treatment of Mm-infected zebrafish with VEGF pathway inhibitors SU5416, a tyrosine kinase inhibitor, or pazopanib, a VEGF receptor inhibitor, reduced bacterial loads and dissemination. Both drugs also synergized with first-line anti-mycobacterial drugs rifampicin and metronidazole, a drug that targets hypoxic bacteria. Inhibiting vascular leakage rather than angiogenesis may be equally efficacious to limit nutrient supply to mycobacteria. During Mm infection, angiopoietin-2 (ANG2) is robustly induced in granulomatous lesions. ANG2 antagonizes ANG1, which promotes vessel stability while limiting angiogenesis and vascular leakage. Indeed, AKB-9785, a molecule that mimics functions of ANG1, reduced vascular leakage and bacterial burden in a Mm zebrafish infection model. Thus, inhibition of angiogenesis is an interesting target for HDT to enhance drug delivery to the site of infection and combined with other therapies is likely to be even more potent.

6 | PERSONALIZED AND COMBINATORIAL HDT

Although HDT could be considered as stand-alone therapy, for example, in patients suffering from total drug-resistant TB, HDT is primarily envisaged as adjunct therapy in combination with classical antibiotics. HDT might be co-administered for a limited duration at the initiation of the standard of care regimens to shorten treatment length and reduce dosage of antibiotics to minimize side effects, or toward the end of treatment to boost host immunity to prevent potential relapse. Consequently, investigating the interactions between HDT and conventional chemotherapy is pivotal, but has only been reported for a limited number of HDTs. Furthermore, in case of undesired interactions between TB drugs and drugs for TB comorbidities (eg, between rifampicin and anti-HIV therapy or anti-diabetic drugs), HDT might be used to shorten current treatment regimens or possibly partially replace components of the conventional chemotheraphy cocktail. In line with this, interactions between HDT and drugs used to treat TB comorbidities should also be investigated thoroughly.

Rather than targeting one specific aspect of the inflammatory response during mycobacterial infections, we hypothesize that correcting the overall immunological disbalance likely is most promising. Type-I IFN and IL-1β signaling, regulating levels of anti-inflammatory prostaglandins and pro-inflammatory leukotrienes, respectively, play an important role in regulating the immune balance during mycobacterial infections. At the time of writing, multiple randomized controlled trials investigate targeting of (one of) these pathways by HDTs.
As some TB patients suffer from overactive type-I IFN/leukotriene signaling while others are characterized by overactive IL-1/prostaglandin activity, we postulate that in this context personalized HDT would be safest and most efficacious. However, this will increase therapeutic costs, which could make such therapy stratifications less attractive and feasible in lower resource settings. To be able to predict whether patients would benefit from a certain HDT, biomarkers monitoring the (immunological) status of patients may need to be identified and developed. This, however, may not be required for all HDTs as some HDT may improve anti-mycobacterial immunity in all patients. As mycobacteria modulate host immunity via many different pathways, a multi-targeted approach could be necessary to fully counteract mycobacteria-mediated host modulation. To our knowledge, however, only two combinations of HDT treatments have been published; combining vitamin-D with PBA did not mediate additive effects compared to solo therapy, likely because both compounds target the same pathway, while in another in vitro study combining protein-kinase A/B inhibitors H-89 or 97i with HDAC inhibitors revealed additive effects in vitro in reducing bacterial load in primary human macrophages.

Modulating (auto-)phagosome maturation using receptor tyrosine kinase inhibitors including imatinib, AZD0530, and multiple repurposed drugs recently identified in our own group has been shown to improve mycobacterial clearance by human macrophages in vitro. Importantly, releasing the mycobacteria-mediated arrest in (auto-)phagosome maturation likely benefits both patients with active disease as well as individuals with latent infection. Above, we have reviewed multiple HDT candidates that enhance autophagy-mediated bacterial clearance. Which of these will be most efficacious against mycobacteria should ideally be determined in head-to-head comparisons. Metformin, being the most frequently investigated, has already been shown to reduce TB recurrence and bacterial loads in patients, and in addition to its effects on autophagy, also enhances mitochondrial membrane polarization, which could further enhance its efficacy.

As discussed above, host-cell death pathways are actively exploited by mycobacteria to promote their survival and dissemination and have been shown to be a potential target for HDT in multiple in vitro and animal studies. Active clinical modulation of (programmed) cell death in patients, however, could lead to significant adverse effects given the complex time- and context-dependency of this mechanism during mycobacterial infection.

Targeting metabolic pathways has been shown to be feasible and represents an attractive target for HDT. While most metabolic pathways are also necessary for host-cell energy production, intracellular lipid accumulation in lipid droplets seems to mainly benefit the intracellular survival of mycobacteria. Preventing or reducing lipid droplet formation in macrophages and concomitant impaired immunity can be mediated by (a) limiting oxidative phosphorylation by, for example, stimulating polarization of macrophages toward pro-inflammatory M1-macrophages, (b) improving/maintaining mitochondrial membrane potential using small molecule M1 or NAD and/or (c) blocking cellular cholesterol uptake using, for example, ezetimibe, which also inhibits phagosomal escape by mycobacteria. Targeting metabolism with HDT may also help correcting the balance between prostaglandins and thromboxanes, as lipid droplets and cytosolic TCA intermediates are the most important sources of eicosanoids.

Irrespective of what causes defective mycobacterial clearance, improving drug delivery to the site of infection likely benefits all TB patients. Angiogenesis in granulomas is significantly impaired and further enhances hypoxia and nutrient-limitation. Targeting angiogenesis during TB by (a) inhibiting VEGF (bevacizumab), (b) inhibiting VEGF-mediated signaling (SU5416 or pazopanib), or (c) antagonizing pro-angiogenesis growth factor ANG2 (AKB-9785) has all been shown to enhance both drug delivery and oxygenation within granulomas in animal models of TB, and may be promising HDTs in combination with other therapies. Despite being most frequently investigated in combination with antibiotics, efflux pump inhibitors could also improve drug delivery of HDTs. To our knowledge, however, this has not been investigated so far but verapamil, known to enhance the efficacy of rifampicin and bedaquiline against different mycobacterial infections, both in vitro and in mice, and also chloroquine and piperman are interesting molecules for combinatorial HDT.

Given their central and important role in orchestrating a functional anti-mycobacterial immune response, restoring (CD4 Th1/17) T-cell immunity has been pursued in many investigations. In addition to enhancing activation of antigen-presenting cells, HDTs that promote phagosomal bacterial degradation (ie, stimulating autophagy, enhancing phagosome maturation and promoting (auto-)phagolysosome fusion) are all expected to enhance presentation of bacterial-derived peptides and thereby improve adaptive immunity. Modulating T-cell responses to restore immunity can be mediated by vaccination or T-cell cytokine therapies. Administration of IL-12 or IL-24 or blocking Th2 cytokine IL-4 promotes Th1 responses with lasting IFN-γ production that may be preferred over IFN-γ administration. Which of these strategies is (most) efficacious and which patients benefit most from this therapy remains to be addressed.

While most of the evidence available for host-pathogen interactions and HDT are from TB studies, the limited number of NTM experimental models investigating host modulation and/or HDT emphasizes the need and urgency to understand NTM pathogenesis as well as identify potentially relevant host targets. Together, these studies will help assess the safety and efficacy of HDT, paving the way for the introduction of HDT against a wide range of mycobacteria.

7 | SEARCH STRATEGY AND SELECTION CRITERIA

We searched PubMed (MEDLINE) for all relevant studies published from 1 January 2000 until 1 October 2020. The medical subject headings used were "host directed", "HDT", "adjunctive", "immunotherapeutic" or "immunomodulation" combined with
“mycobacterium”, “mycobacteria”, “tuberculosis”, “nontuberculous” or “NTM”. All relevant abstracts were screened independently by two researchers. The final reference list was generated based on relevance to the topics covered in this review. Only papers published in English were included.

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CONFLICT OF INTEREST
All authors declare no competing or conflicting interests.

DATA AVAILABILITY STATEMENT
Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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