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Host Immune-Metabolic Adaptations Upon Mycobacterial Infections and Associated Co-Morbidities

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Mycobacterial diseases are a major public health challenge. Their causative agents include, in order of impact, members of the *Mycobacterium tuberculosis* complex (causing tuberculosis), *Mycobacterium leprae* (causing leprosy), and non-tuberculous mycobacterial pathogens including *Mycobacterium ulcerans*. Macrophages are mycobacterial targets and they play an essential role in the host immune response to mycobacteria. This review aims to provide a comprehensive understanding of the immune-metabolic adaptations of the macrophage to mycobacterial infections. This metabolic rewiring involves changes in glycolysis and oxidative metabolism, as well as in the use of fatty acids and that of metals such as iron, zinc and copper. The macrophage metabolic adaptations result in changes in intracellular metabolites, which can post-translationally modify proteins including histones, with potential for shaping the epigenetic landscape. This review will also cover how critical tuberculosis co-morbidities such as smoking, diabetes and HIV infection shape host metabolic responses and impact disease outcome. Finally, we will explore how the immune-metabolic knowledge gained in the last decades can be harnessed towards the design of novel diagnostic and therapeutic tools, as well as vaccines.

Keywords: mycobacteria, macrophage, immunometabolism, host-directed therapies, tuberculosis

INTRODUCTION

Mycobacteria have been a major cause of human disease for millennia, with the effects of *Mycobacterium tuberculosis* (*M.tb*) seen in the skeletons of mummified human remains from over 4000 years ago (1). The main mycobacteria of public health importance today are members of the mycobacterium tuberculosis complex (which includes *M.tb, M.bovis, M.africanum, M.microti, M.pinnepedi, M.caprae*), which cause tuberculosis (TB), *Mycobacterium leprae* (*M.leprae*) the cause

of leprosy, and nontuberculous mycobacteria (NTM) leading to a wide variety of clinical presentations. NTM include *Mycobacterium ulcerans* (*M.ulcerans*), the cause of Buruli ulcer (BU).

Around 2 billion people worldwide are infected with *M.tb*. Approximately 10 million people fall ill with TB each year and there are around 1.5 million deaths (2). Great progress has been made with TB control over the past decade, but these gains have been undermined to some extent by the ongoing Covid-19 pandemic, especially in less well-resourced settings (3). Current treatment for drug sensitive TB is a minimum of 6 months and considerably longer for drug resistant disease. Shorter more effective treatments are needed, and host-directed therapies (HDT) arise as a promising strategy.

Leprosy caused by chronic infection with *M.leprae* is predominantly a disease of the skin and peripheral nerves. It is curable with a prolonged course of antibiotics. The incidence of leprosy has declined over the past century, but the rate of decline is currently sluggish. A large proportion of endemic countries (118/161) reported new cases in 2019 (202,256 or 26 per million population) (4). Although antibiotics can still cure the disease, permanent changes to nerves can occur leading to lifelong disabilities. There is still a great amount of stigma around the diagnosis of leprosy which can delay detection and effective treatment. Also, weak health systems can make early detection and treatment difficult. Current therapies although effective are prolonged and commonly associated with adverse effects (5).

Both TB and leprosy present a spectrum of clinical manifestations. TB can be described as a dynamic continuum from asymptomatic *M.tb* infection to active infectious disease, including latent infection as well as incipient, subclinical and active TB disease (6, 7). Leprosy also comprises ample clinical variability. The two extremes of the spectrum are tuberculoid and lepromatous forms of the disease, the first being paucibacillary and mild, while the latter is multibacillary and presents increased disease severity (8, 9).

There are over 200 species of NTM identified to date (10), of which the vast majority (over 95%) have not been associated with human disease. NTM are predominantly environmental organisms of low pathogenicity to humans that only cause disease in specific circumstances. An exception is *M.ulcerans*, which causes chronic skin ulcers in immunocompetent individuals, through production of a diffusible cytotoxin called mycolactone (11). BU is, after TB and leprosy, the third most common mycobacterial disease worldwide and together with leprosy one of the 20 Neglected Tropical Diseases prioritized by the WHO (12). West African countries are the worst impacted by BU, with prevalence rates reaching 26.9 cases per 10,000 in Benin. Other NTMs primarily affect immunocompromised people. Recently, NTM infections have been associated with health care procedures with infections due to *M.chimerae* occurring after cardiac surgery (13) and infections with rapid growing NTM's such as *M.abscessus* being associated with cosmetic surgery procedures (14). *M.abscessus* is also associated with progressive lung infection in patients with cystic fibrosis (15). Treatment of NTM infections is complex requiring multiple prolonged antibiotics which may not be effective or well tolerated. Overall, novel treatments for mycobacterial diseases are needed. HTDs are a promising approach but we need a greater understanding of how the host responds to infection.

MACROPHAGES AS TARGETS OF MYCOBACTERIAL INFECTION

Macrophages not only play an essential role in the host immune response to mycobacteria, but they also are mycobacterial targets. They fulfil a variety of essential functions in homeostasis and disease, including phagocytosis, uptake and killing of pathogens, tissue repair and inflammation resolution (16, 17). Mirroring their wide range of functions, macrophages constitute a highly diverse and heterogeneous population (18, 19). Traditionally, they have been classified into M1, i.e. classically-activated (LPS + IFNγ) and pro-inflammatory, and M2, i.e. alternatively-activated (IL-4) and anti-inflammatory. While the oversimplified M1/M2 dichotomy has been a useful tool when studying macrophage diversity, most macrophages exist as a spectrum and contain features of both (20, 21). Additionally, it is increasingly recognised that specific environmental cues can promote certain macrophage phenotypes and functions, demonstrating their plasticity. Metabolically, M1-like macrophages are predominantly glycolytic and present a broken TCA cycle (22). Their pentose phosphate pathway as well as fatty acid synthesis are highly active, ensuring availability of biosynthetic precursors. In contrast, M2-like macrophages mainly rely on oxidative metabolism, present an intact TCA cycle and fatty acid oxidation is upregulated. This review will explore macrophage metabolic diversity and flexibility and how these metabolic changes can drive specific phenotypes and functions, focusing on their relevance in the context of mycobacterial pathogenesis.

M.tb infection occurs when aerosols containing the bacilli are inhaled by a susceptible host. When *M.tb* reaches the lung, alveolar macrophages (AM), the first cellular target (23), are infected. Infected AMs can migrate to the lung interstitium, facilitating infection of other cell types, including newly-recruited monocyte-derived macrophages and neutrophils. Although abundant evidence points towards *M.leprae* being transmitted through the respiratory route (24, 25), the precise mechanisms for *M.leprae* spread remain to be fully elucidated (26). *M.leprae* primary cell targets are macrophages and Schwann cells, the latter contributing to build the myelin sheath that covers nerve fibres. Following introduction into the skin, *M. ulcerans* bacilli are phagocytosed by macrophages and multiply intracellularly until bacterial production of mycolactone causes host cell apoptosis (11, 27). Therefore, macrophages are a clear target for mycobacterial pathogens which have evolved successful strategies to survive and replicate within them (28), including metabolic manipulation.

In the context of mycobacterial disease, macrophages play an essential role in driving innate and adaptive immune responses

and inflammation, while mediating both tissue destruction and repair (29). Two major macrophage populations cohabit in the lung: AMs and interstitial macrophages (IMs). They are distinct at the ontogenic, phenotypic, metabolic and functional levels (30). AMs display an M2-like phenotype (31) with predominant oxidative metabolism (30, 32), similar to IL-4 treated hMDM (33). In contrast, IMs are mainly derived from recruited monocytes (34, 35), and this has been particularly shown in the context of *M.tb* infection (30, 36). IMs are M1-like and operate at high levels of glycolysis (30). Other types of macrophages relevant in the context of mycobacterial infection include epithelioid cells, multinucleate giant cells (MGCs) and foamy, lipid-rich macrophages (37). MGCs are the result of macrophage fusion within the granuloma, organised cellular aggregates hallmark of TB and leprosy (38).

In leprosy, skin lesions from the milder, tuberculoid forms of the disease have been shown to have an M1-like macrophage predominant population, whereas in more severe skin lesions of multibacillary patients the balance shifts towards M2-like macrophages (39).

BU manifests as chronic ulcerative skin lesions with a distinctive lack of pain and inflammation, which if untreated enlarge over time (40). Tissue necrosis, local analgesia and defective inflammation are all attributed to bacterial production of mycolactone, a diffusible macrolide targeting the entry point of the secretory pathway in eukaryotic cells: the Sec61 translocon (11, 41, 42). By inhibiting Sec61, mycolactone prevents host cell's production of secreted proteins, and most of its transmembrane proteins, leading to their cytosolic degradation by the proteasome (43–45). In the skin regions surrounding bacterial foci, complete and sustained inhibition of Sec61 in host cells triggers endoplasmic reticulum (ER) stress responses culminating in apoptosis (46). In immune cells recruited to the site of infection, including macrophages, exposure to non-cytotoxic concentrations of mycolactone prevents the production of cytokines, chemokines and the transduction of receptor-mediated signals, thereby the generation of protective immune responses (41). How *M.tb*, *M.leprae* and *M.ulcerans* impact the metabolic reprogramming of immune cells is explored in the following section, and is summarised in **Table 1**.

IMMUNE-METABOLIC ADAPTATIONS OF THE MACROPHAGE TO MYCOBACTERIAL INFECTION

This section provides an overview of the current knowledge regarding the effects of *M.tb*, *M.leprae* and *M.ulcerans* on host macrophage glycolysis, oxidative and lipid metabolism (**Figure 1**).

Glycolysis Versus Oxidative Metabolism: Shaping Macrophage Polarisation

Activation of Toll-like receptors (TLRs) by mycobacterial components induces dynamic and coordinated changes in the energy metabolism of host macrophages similar to those occurring during macrophagic differentiation into the M1-like phenotype. They include a switch towards glycolysis, a disruption of the TCA cycle leading to the accumulation of succinate, and an impaired oxidative phosphorylation. Such alterations are promoted by the Hypoxia-Inducible Factor (HIF)-1α, an oxygen sensor and key glycolysis regulator that is activated by the TCA cycle intermediate succinate and mediates the production of Interleukin (IL)-1β (56). Induction of aerobic glycolysis and HIF-1α are beneficial for both innate and IFNγ-dependent control of intracellular *M.tb* infection by host macrophages (47, 57, 58). Importantly, in contrast to killed *M.tb* and the vaccine strain Bacille Calmette-Guérin (BCG), live *M.tb* was recently shown to specifically prevent the glycolytic switch in infected macrophages, pointing towards *M.tb* having evolved specific strategies to modulate host cell metabolism to its own benefit (48–50). Thus, there is an arms race to control macrophage metabolism as it is essential in determining infection outcome, and this topic has been extensively covered in recent excellent reviews (59–61). Validating this idea, it was shown in a mouse model of *M.tb* infection that ontologically and metabolically distinct lung

TABLE 1 | M1-like vs M2-like macrophages in mycobacterial infection.

	M1-like	M2-like
Baseline	Predominantly glycolytic Pro-inflammatory Microbicidal Key markers: CD86, iNOS, ROS	Mainly reliant on oxidative metabolism Anti-inflammatory Tissue repair Key markers: CD206, CD163, Arg
M.tb	Interstitial macrophages Glycolysis needed for *M.tb* control (47) *M.tb* restricts glycolysis (48–50)	Alveolar macrophages More permissive to *M.tb* growth (30)
M.leprae	Predominant tuberculoid, lesions (39, 51) Blocks M1 polarization in infected monocytes (52)	Predominant in severe lesions (39, 51) Favor bacterial persistence (53) Infections promote M2 phenotype in hMDMs (54, 55) Promotes Treg phenotype (54, 55)

Summary of the key distinctive factors between the M1-like and M2-like macrophage populations. Each population plays a different role in the context of M.tb and M.leprae infection, and have specific capabilities to combat infection, resulting in differential outcome.

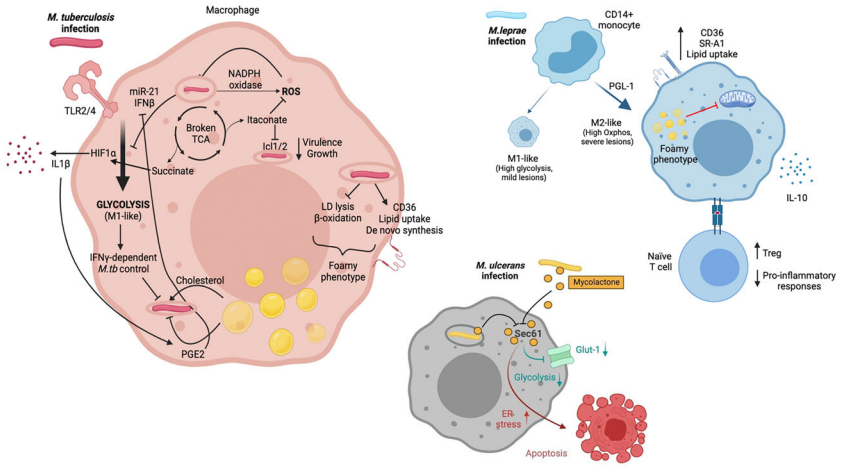

FIGURE 1 | *M.tb*, *M.leprae* and *M.ulcerans* infect macrophages and alter their metabolism. *M.tb* is primarily sensed by host macrophages through TLR2 and TLR4. Macrophage metabolism shifts towards glycolysis (M1-like), which allows infection control. *M.tb* has developed strategies to counteract this metabolic switch though induction of miR-21 and IFNβ. M1-like macrophages present a broken TCA cycle, with elevated succinate concentrations that stabilise HIF1α, essential for induction of glycolysis and secretion of pro-inflammatory cytokines such as IL-1β. Itaconate also arises as a consequence of a broken TCA cycle and has multiple immune-regulatory functions, including inhibition of isocitrate lyases Icl1/2. *M.tb* infection triggers ROS production through NAPDH oxidase. It also promotes increased intracellular lipid content. This results in the development of lipid droplets and the foamy macrophage phenotype, which can be beneficial (i.e. providing cholesterol as nutrient) or detrimental (i.e. secretion of prostaglandins) for the pathogen. *M.leprae* infection of CD14+ monocytes drives macrophages towards an M2-like phenotype, with a key role for PGL-1. M2-like macrophages rely on oxidative metabolism and are associated with severe lesions. Upon *M.leprae* infection, macrophages upregulate CD36 and SR-A1 which translates in increased lipid uptake. Lipid droplets and the foamy phenotype have been linked to suppressed mitochondrial function. Furthermore, *M.leprae*-infected macrophages promote a Treg phenotype when interacting with naïve T cells, together with an impairment of pro-inflammatory cytokine release. Mycolactone released by phagocytozed and extracellular *M. ulcerans* bacilli diffuses into the cytoplasm of host macrophages and neighboring cells, respectively, gains access to the Sec61 translocon and blocks its activity. An immediate effect of Sec61 blockade by mycolactone is the downregulation of secretory and transmembrane proteins, among which the glucose importer Glut-1, likely resulting in decreased glycolysis. Sustained Sec61 blockade in mycolactone-exposed cells, including macrophages, triggers ER stress responses culminating in apoptosis. *Created with BioRender.com.*

macrophage populations (AMs and IMs) have differential capacities to control bacterial burden (30). Specifically, IMs which are predominantly monocyte-derived and glycolytic, present an increased ability to control *M.tb* growth compared to AMs, a subset of embryonic origin committed to fatty acid oxidation. Although these findings require further validation in humans, a recent single cell RNA-seq study demonstrated that the majority of lung macrophage populations are conserved between mouse and human (62).

Reprogramming of energy metabolism in *M.tb*-infected macrophages is also associated with increased levels of NADPH oxidase and inducible nitric oxide synthase (iNOS), promoting the production of reactive oxygen species (ROS) including nitric oxide (NO) with antimycobacterial activity (63, 64). In addition to yielding succinate, disruption of the TCA cycle upon *M.tb* infection promotes the generation of itaconate from cis-aconitate by aconitate decarboxylase, also known as immune-responsive-gene 1 (IRG1). Although itaconate suppresses the production of inflammatory cytokines and ROS by infected macrophages (65, 66), it directly inhibits *M.tb* enzymes isocitrate lyases Icl1/2, which are required for bacterial virulence and growth *in vivo* (67). IRG1 expression was shown to potentiate macrophage capacity to control intracellular *M.tb* (68) and prevent immunopathology in a mouse model of *M.tb* infection (69), demonstrating the key importance of this metabolic pathway in host defence against *M.tb*.

Studies in Schwann cells suggested that infection with *M.leprae* may also triggers major metabolic reprogramming in infected macrophages. Following infection by *M.leprae*, Schwann cells increase the expression of insulin-like growth factor (IGF), upregulating glucose transporter 1 (GLUT-1) and glucose uptake by Akt signalling (70). Glucose is redirected from glycolysis to the pentose phosphate pathway through the activation of G6PD, increasing the carbon flux to lipid biosynthesis, while both mitochondrial activity and lactate production are reduced (71, 72). Since *M.leprae* infection success depends on the pentose phosphate pathway, which generates reducing power for glutathione antioxidant system, it was proposed that *M.leprae* subverts host cell glucose metabolism to facilitate glutathione regeneration and thereby free-radical control (71).

In vitro experiments demonstrated that M1-like macrophages acquire M2-like phenotypes in the presence of *M.leprae* and apoptotic cells (which occur in skin lesions), contributing to mycobacterial persistence (52). Exposure of human CD14+ monocytes to *M.leprae* (MOI 5:1) inhibited M1 polarization, and this effect was likely mediated by the lipid component PGL-1 (73). IL-10 (anti-inflammatory) and IL-15 (pro-inflammatory) were shown to drive distinct macrophage responses which translated into progressive versus self-healing leprosy lesions,

respectively (54). Live (but not killed) *M.leprae* promoted an M2-like phenotype in hMDM, based on IL-1β, IL-6, TNF, IL-10, CD163 and MHC-II expression (55). This M2-skewing was confirmed by measuring IL-10 and IL-12 transcript and protein levels in a different study (74). When *M.leprae*-infected macrophages were exposed to naïve T cells, diminished pro-inflammatory responses together with increased T regulatory phenotypes were reported (55, 74). These changes occurred using *M.leprae* harvested from both tuberculoid and lepromatous skin lesions (74). These findings suggest that the M2-like macrophages with predominant oxidative metabolism – same as in the context of *M.tb* infection - would favour pathogen persistence rather than infection resolution.

Production of mycolactone by intracellular *M.ulcerans* causes the apoptosis of host macrophages, and bacteria grow primarily extracellularly in infected skin during active BU (11). However, mycolactone released by bacteria diffuses broadly in infected organisms, interfering with the metabolism of both skin-resident and more distant cells (11, 75–77). Mycolactone-mediated Sec61 blockade is likely to impair host cell energy metabolism *via* the downregulation of nutrient tranporters, such as the glucose transporter Glut1 (SLC2A1). In support of this hypothesis, our metabolomic analysis of Jurkat T cells exposed to mycolactone revealed decreased intracellular levels of Glut1 substrates, glucose-1-phosphate and mannose-6-phosphate, suggesting impaired glycolytic activity (77). We speculate that during infection with *M.ulcerans*, inhibition of Sec61 impairs glycolysis reprogramming in infected macrophages, and more generally in all mycolactone-exposed immune cells.

Lipid Metabolism

In addition to reprogramming energetic metabolism, *M.tb* infection rewires the lipid metabolism of host macrophages through inhibition of catabolic pathways (lipid droplet [LD] lysis and β-oxidation of fatty acids) and concomitant activation of lipid uptake, mobilization and *de novo* synthesis (78). This leads *M.tb*-infected macrophages to acquire a foamy phenotype, due to the cytoplasmic accumulation of LDs mainly composed of triacylglycerol (TAGs), a storage form of fatty acids, and cholesteryl esters. Whether LD accumulation is beneficial to host macrophages or intracellular *M.tb* is a matter of debate. Since intracellular *M.tb* has the ability to import fatty acids deriving from host TAGs and foamy macrophages are a hallmark of chronic TB, accumulation of LDs in infected macrophages may provide the pathogen with essential nutrients (37, 79–81). However, recent data indicate that LD maintenance requires IFNγ-driven induction of HIF-1α, which inhibits lipolysis and prevents *M.tb*'s acquisition of host lipids (82). Besides, LDs are the major sites of eicosanoid production including the anti-mycobacterial prostaglandin E2 (PGE2) (83), and have direct antibacterial properties (84). PGE2 is required for *M.tb* control (85, 86) Leukotriene B4 (LTB4) is elevated in pulmonary TB compared to latent *M.tb* infected individuals (LTBI) (87) and contributes to *M.tb* immunopathogenesis (86). Beside eicosanoids, fatty acids released by LD lysis can be shuttled across the mitochondrial cell wall for β-oxidation, generating acetyl-CoA that enters the TCA cycle, and co-enzymes used in the respiratory chain to produce ATP. Interestingly, inhibiting fatty acid oxidation augmented macrophage ability to control *M.tb* infection (30, 53). Rather than starving intracellular *M.tb* from lipid nutrients, blocking β-oxidation of fatty acids may favour the generation of mitochondrial ROS that promote the phagosomal recruitment of NADPH oxidase and the xenophagic elimination of *M.tb* (53).

Similar to *M.tb*, *M.leprae* upregulates lipid uptake and biosynthetic pathways in infected macrophages, particularly cholesterol (88, 89). Mechanistically, infection with *M.leprae* increases macrophage expression of scavenger receptor (SR)A-I and CD36, promoting the foamy macrophage phenotype (90, 91). The mycobacteria seem to take shelter within lipid bodies, formed abundantly by host cells, possibly as a strategy to cover and hide surface antigens from innate immune receptors in the cytosol (92, 93). Contrary to *M.tb* (94), *M.leprae* cannot degrade or utilize cholesterol as a nutritional source (92), leaving the mechanism by which host cholesterol metabolism supports its *in vivo* persistence undefined. Notably, *M.leprae* infection reduces host cell mitochondrial activity in a distinctive manner (88). Oliveira et al. proposed that cytosolic accumulation of lipids in *M.leprae*-infected macrophages may contribute to mitochondrial shutdown and suppression of their innate immune functions (88).

Besides, macrophages infected with *M.tb* deprive intracellular bacteria from essential micronutrients like iron and manganese, while using copper and zinc to poison them (95). In turn, *M.tb* has developed sophisticated strategies to ensure micronutrient acquisition and resist metal toxicity. Interestingly, iron release prevails in AMs facilitating *M.tb* access to iron, whereas IMs have the capacity to sequester it, contributing to an iron starvation *M.tb* phenotype (96). Further information on this topic can be found in an excellent recent review by Neyrolles et al. (95). Proteins involved in iron uptake and metabolism are upregulated in lepromatous leprosy lesions, compared to tuberculoid forms, suggesting an association between iron storage in *M.leprae*-infected macrophages and intracellular bacterial persistence (97).

Together, these studies revealed aerobic glycolysis and fatty acid oxidation as key metabolic pathways enhancing or decreasing the anti-mycobacterial responses of macrophages, respectively. They highlighted species-specific mechanisms used by *M.tb*, *M.leprae* and *M. ulcerans* to subvert the glycolytic switch that is induced by TLR stimulation in infected macrophages, and take advantage of the increased lipid anabolism in host macrophages.

METABOLIC-EPIGENETIC CROSSTALK IN MYCOBACTERIAL-INFECTED MACROPHAGES

The macrophage metabolic adaptations to mycobacterial infection translate into changes of the intracellular metabolome. The concentration of particular metabolites therefore increases with the predominance of certain metabolic pathways. For example, lactate generation is enhanced with glycolysis, and so are citrate and acetyl-CoA with an active TCA cycle. These metabolic intermediates have the potential to

post-translationally modify a wide range of proteins (e.g. histones), increasing proteome diversity and modulating function, including immune function, according to the cell needs (98–100). DNA and histones can thus be modified through metabolic substrates (e.g. methionine, acetyl-CoA, lactate), and metabolic genes can also be targets of such modifications (101). There is increasing recognition that epigenetics play an important role in shaping host-pathogen interactions and infection outcomes.

Zhang and colleagues showed that macrophage histones can be lactylated promoting an M2-like phenotype upon bacterial challenge (102), although this idea has been recently challenged (103). Since elevated glycolysis and lactate production occur in the lung of *M.tb*-infected hosts [reviewed in (104)], lactate could potentially drive macrophages towards an M2-phenotpye, favouring *M.tb* survival.

M.tb components switch host cellular metabolism toward aerobic glycolysis in human peripheral blood mononuclear cells (PBMC) through a TLR2-dependent but NOD2-independent mechanism which is partly mediated *via* the activation of the AKT/mTOR pathway (58). This seems to be of functional relevance as inhibition of the AKT/mTOR pathway inhibits cellular responses to *M.tb* both in human PBMC and a murine model of TB (58). Insights into the possible mechanisms underlying this relationship has come from studies of BCG vaccination, which has been shown to be a potent inducer of trained immunity due to cellular metabolism reprogramming arising from epigenetic changes (105). BCG-stimulated monocytes have been shown to undergo chromatin remodeling due to histone modification, namely increases in H3K4me3 and H3K9me3 at promoter sites of essential glycolytic genes. The resultant activation of the AKT/mTOR/HIF-1α pathway switches cellular metabolism from oxidative phosphorylation to aerobic glycolysis and as a consequence facilitates increased production of cytokines such as TNF and IL-6 that promote mycobacterial killing (106, 107). Conversely, these epigenetic changes are dependent on the induction of metabolic processes, as inhibition of glycolysis results in reversal of changes in H3K4me3 and H3K9me3 at promoter sites of TNF and IL-6 (107). In contrast to BCG, *M.tb* has been shown to impair macrophage trained immunity through activation of the type I interferon/iron axis in hematopoietic stem cells (108). This immune-metabolic reprogramming also resulted in suppressed myelopoiesis, overall enhancing host susceptibility to *M.tb* infection (108).

Another recently described epigenetic modification shown to cause immunomodulation in *M.tb* infection involves Alu repeat elements. Alu repeats are mobile interspersed repetitive DNA sequences that are transposable from one site in the genome to another, resulting in mutations, insertions and recombination events in protein-coding mRNAs (109). Analysis of genes adjacent to H3K4me1-associated Alu repeats linked to macrophage metabolic responses to *M.tb* infection has shown that Liver X Receptor-α signaling can be initiated at response elements present in Alu repeats and significantly reduces *M.tb* viability by altering cholesterol metabolism and enhancing macrophage apoptosis (110). Furthermore, levels of *Alu* methylation have been found to be significantly lower in paediatric TB patients and the detection of *Alu* DNA methylation may serve as a diagnostic and prognostic tool of TB disease in this population (111).

CO-MORBIDITIES IMPACT ON METABOLISM AND IMMUNITY

Vulnerability to infection with *M.tb* and progression to active disease can be affected by several co-morbidities and social risk factors. The main co-morbidities associated with TB progression and poor outcomes are HIV infection, diabetes, renal disease and smoking. Social risk factors such as excess alcohol consumption, air pollution, incarceration and poor housing are also important. Diabetes, tobacco smoking and HIV infection have a profound impact on the host metabolic state, at both the macrophage (**Figure 2**) and systemic levels. Understanding how these metabolic changes occur will contribute to elucidating why these particular conditions worsen TB.

Smoking

The fact that tobacco smoking impacts the immune system and increases the prevalence of both respiratory and distal organ-associated diseases has been known for decades [reviewed in (112–116)]. Cigarette smoke (CS) contains abundant

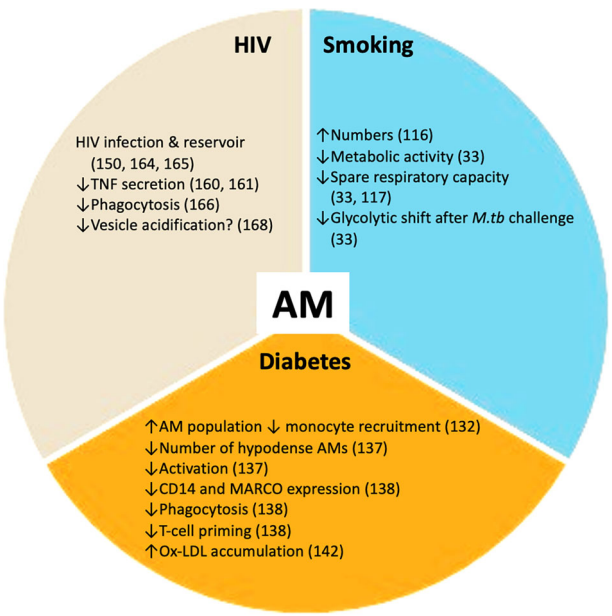

FIGURE 2 | TB co-morbidities impact alveolar macrophages (AMs). Smoking, HIV infection and diabetes mellitus perturb the healthy alveolar macrophage phenotype. These co-morbidities promote changes in alveolar macrophage metabolism and essential functions including phagocytosis and cytokine secretion. These disturbances render the alveolar macrophage population more susceptible to *M.tb* infection. ↑ increased; ↓ decreased.

compounds (including toxins and carcinogens) which can directly modify immune function [reviewed in (115)].

Few studies have investigated the direct metabolic impact of smoking in *M.tb* infection. A macrophage shift to glycolysis is essential for effective control of *M.tb* (30, 47, 49). AMs from smokers presented decreased capacity to control H37Ra *M.tb* compared to non-smokers (117). This was probably due to impaired secretion of key cytokines for infection control, including IL-1β, TNF and IFNγ, and some of these altered immune responses remained in AMs from ex-smokers (117).

Both reduced metabolic activity (measured by oxygen consumption rate [OCR] and extracellular acidification rate [ECAR]) and metabolic reserves (glycolytic reserve and spare respiratory capacity [SRC]) have been reported at baseline in AM from smokers, measured by extracellular flux analysis (33). Interestingly, baseline metabolism of smokers' AMs was skewed towards glycolysis, matching previous results (118). AMs from smokers showed diminished glycolysis than AMs from non-smokers when challenged with *M.tb*, measured by extracellular flux analysis and lactate secretion (33). No differences in oxidative metabolism were detected. Of note, the essential shift towards glycolysis (ECAR/OCR) for *M.tb* control was severely impaired in smokers' AMs compared to their non-smokers counterparts, and was confirmed at the transcriptional level (2-fold change reduction in the glycolysis rate-limiting enzyme hexokinase 1). This translated in a trend towards attenuated pro-inflammatory responses (IL-1β and PGE2 secretion). The described deficient shift to glycolysis, decreased lactate and IL-1β secretion were confirmed in an *in vitro* model of hMDMs treated with CSE (33). The bioenergetic profiling experiments were performed using H37Rv γ-irradiated *M.tb*. This is important since live/dead *M.tb* have been shown to induce profoundly different metabolic adaptations in hMDMs measured by extracellular flux analysis (48). Other studies using hMDM and a THP-1 model and CSE have shown impaired responses to LPS, based on reduced basal and induced glycolysis, NLRP3 activation and subsequent IL-1β and IL-18 secretion (119).

Although further mechanistic studies are needed, there is enough evidence supporting the notion that CS causes dysfunctional AM metabolic profiles, which directly impact the orchestration of effective immune responses against respiratory pathogens, and might help explaining the worsening of TB reported in the smoking population.

Diabetes Mellitus

The Increasing Overlap of Two Epidemics

Up until a few years ago, the epidemics of TB and diabetes mellitus (DM) were, for the most part, geographically disconnected. Today, the geographic overlap between these two epidemics arises as a worldwide threat, as TB and diabetes have the potential to make each other worse (120, 121). It is estimated that about 15% of current TB cases are associated with T2D (122, 123). Here, we will discuss how diabetes detrimentally impacts TB.

Animal studies have further confirmed that DM worsens TB outcomes. In a mouse model of DM using streptozotocin (STZ) to destroy pancreatic islets, macrophages presented a 90% reduction in their phagocytic capacity, although their intracellular killing abilities were intact (124). When these mice were challenged with *M.tb* (Schacht strain) 90% of them died, compared to 10% in the non-diabetic group (124). Other mice, rat and guinea pig models of diabetes/hyperglycaemia have reported increased bacterial burden compared to control animals, together with diminished IFNγ responses (125–129).

Immune Alterations

Chemotaxis of monocytes has been shown to be impaired in diabetic patients (130, 131), potentially affecting recruitment into the lung. Furthermore, monocytes from DM patients presented diminished binding and phagocytic capacity towards H37Rv *M.tb* compared to healthy controls (132).

Within the lungs of diabetic C57BL/6 mice (STZ model) and using an aerosol challenge model of Erdman *M.tb*, it was shown that the increased TB susceptibility may arise from delayed innate immune responses (133). In particular, at 2 weeks post-infection (pi) there was abundant recruited monocytes at the site of infection in the control group. In contrast, in the lungs of diabetic mice, *M.tb*-infected AMs prevailed, and monocyte recruitment was limited (133). This translated in delayed delivery of *M.tb*-antigens to the lymph nodes, and delayed presence of IFNγ+ *M.tb*-specific T cells in the lymph nodes and in the lungs compared to the non-diabetic group, slowing appearance of effective immune responses and potentially contributing to bacterial persistence (133). The mechanisms underlying impaired chemotaxis/recruitment remain unknown. The reliance of AMs on oxidative metabolism which facilitates *M.tb* persistence, in comparison to the more glycolytic recruited monocytes, could further explain the observed differences in mycobacterial control.

PBMCs from healthy individuals treated with *M.tb* lysate in high concentrations of glucose (40mM, but not 25mM or lower) resulted in increased secretion of TNF, IL-1β, IL-6, but not IFNγ IL-17A and IL-22 (134). Differentiated macrophages at 25 mM glucose promoted enhanced cytokine production after stimulation with *M.tb* lysate and LPS. However, no differences were reported in phagocytosis and *M.tb* killing capacities (134). Macrophages differentiated from healthy individuals and diabetic patients were characterised at baseline and after *M.tb* infection (MOI 5:1 for 24h) with different strains (135). Expression of key molecules for antigen presentation (HLA-DR, CD80 and CD86), the inhibitory molecule PD-L1, and cytokines/chemokines secretion patterns differed between DM patients and controls. MDMs from T2D patients presented attenuated capacity to bind, internalise and clear *M.tb*, and worse outcomes were reported with more virulent strains (135). Similarly, MDMs from chronic diabetic patients presented impaired *M.tb* killing capacity (136). Monocytes from T2D patients and healthy controls infected with *M.tb* presented similar bacterial growth (137). However, monocytes cultured at 30mM glucose to mimic hyperglycaemic conditions, compared to monocytes cultured at 11mM glucose, presented decreased IL-8 production (a key neutrophil chemoattractant) as well as increased H37ra *M.tb* survival 3 days pi (137).

In the particular context of AM, TB-DM patients presented decreased numbers of a particular hypodense AM subset, compared to TB only patients (138). Within the active pulmonary TB patients, a negative correlation was observed between the percentage of

hypodense AMs and sputum bacterial load, together with disease severity assessed by chest X-ray. Overall AMs from TB-DM patients were less activated (138). Although primarily reporting descriptive findings, this is, to our knowledge, the first study showing direct impact of DM in the AM lung-resident population. Another key study focusing on AMs used the STZ mice diabetes model and showed that AMs from diabetic mice presented reduced CD14 and MARCO expression, the latter being essential in the recognition of trehalose 6,6′-dimycolate (TDM) within the bacterial cell wall (139). This translated in reduced *M.tb* (Erdman strain) phagocytosis and was specific to the AM population (peritoneal or BMDM did not present this altered phenotype). These AMs defects resulted in impaired T-cell priming, which was observed when AMs from diabetic animals were transferred to control animals (139).

Other major immune cell types including dendritic cells, neutrophils, natural killer cells and T cells are also impacted in the context of diabetes and hyperglycaemia. It is beyond the scope of this review to explore their precise mechanisms, and they have been reviewed elsewhere (140, 141).

Immune-Metabolic Alterations Beyond Hyperglycaemia

DM not only comprises hyperglycaemia but also a wide range of further metabolic alterations [reviewed in (142)] which have the potential to impact immune responses to *M.tb* (i.e. dyslipidaemia, redox and hormone balance). DM is often associated with dyslipidaemia (e.g. increased oxidised-low density lipoproteins [ox-LDLs)] and although it is difficult to establish causal links, it is well described that *M.tb* thrives in lipid-rich environments. Ox-LDLs accumulate in AMs of guinea pigs infected with *M.tb*, increasing bacterial burden (143). Similarly, *in vitro* human studies showed that ox-LDLs promoted *M.tb* survival by impairing lysosomal function (144).

It is challenging to draw conclusive answers regarding the underlying mechanisms of TB enhanced susceptibility in DM patients due to the limited number of human studies and the variety of models used (ie. mouse and human monocytes/macrophages, from diabetic subjects or treated with varying concentrations of glucose). Nonetheless, there is ample evidence suggesting altered function of the myeloid compartment in the context of DM, including chemotaxis, bacterial recognition, phagocytosis, cytokine secretion and metabolism, which could facilitate TB disease. The described immune alterations have the potential to impact the outcome of other infectious diseases [reviewed in (145, 146)]. Although there is scarce literature exploring the link between diabetes and leprosy, early studies reported an increase in diabetes in lepromatous leprosy patients (147).

HIV

According to the WHO, people living with HIV have an increased risk (16-27 times) of developing active TB compared to non-infected individuals (2). One of the key mechanisms behind this enhanced risk is the fact that HIV causes CD4+ T cell depletion [reviewed in (148)], a cell subset essential for control of *M.tb* infection (149–151). There is increasing awareness of HIV-driven impairment in the innate immune compartment as a key contributor to increased TB risk in *M.tb*-infected individuals. Here, we explore the impact of HIV infection on macrophages and how that may facilitate TB progression.

Monocyte chemotaxis (152) and monocyte oxidative burst capacities have been shown to be impaired in HIV-infected individuals (153). HIV infection downregulated essential TLRs in the myeloid compartment which are essential for *M.tb* recognition (154, 155). *In vitro*, HIV infection of hMDMs promotes an M1-like phenotype (156) and impacts macrophage metabolism, inducing mitochondrial fusion, reduced oxidative phosphorylation and no changes in glycolysis (157, 158). Enhanced lipid accumulation together with increased uptake of ox-LDL was reported in hMDMs from HIV-infected individuals compared to controls, which could potentially contribute to the foamy macrophage phenotype and aid *M.tb* survival (159). HIV-infected hMDMs prevented GM-CSF-mediated activation of STAT5A, a signalling pathway essential for TB control (160). TNF secretion was reduced in HIV/*M.tb* co-infected macrophages compared to *M.tb* alone in a THP-1 cell model and human AMs (161, 162), as well as TNF-dependent apoptosis (161–163). There is evidence of HIV capacity to infect AMs (164, 165) which can act as viral reservoirs (166). HIV-infected AMs present impaired phagocytic function (167), and HIV inhibits phagocytosis in hMDMs in a Nef-dependent manner (168). Restricted vesicle acidification in AMs from HIV-TB patients has been reported (169). One study in HIV-TB coinfected individuals reported no differences in phagocytosis or acidification capacities due to HIV infection (170). The overall evidence suggests that HIV makes AMs more permissive to *M.tb* and promotes early bacterial growth, but further research is needed to precisely elucidate the role of macrophage metabolism in this co-infection setting.

In contrast to TB, an increased risk of leprosy or enhanced severe disease has not been described in HIV-infected individuals [reviewed in (171)]. However, leprosy patients receiving highly active antiretroviral therapy (HAART) are at increased risk of reversal reaction (RR), an inflammatory exacerbation (172). The monocyte/macrophage phenotype has been shown to be distinct in skin lesions from RR/HIV patients compared to RR alone (173) including increased expression of CD209, vascular endothelial growth factor (VEGF), arginase 2 (ARG2) and PPARγ in the former. The clinical implications of these findings remain unknown. HIV-BU co-infection is rare and there is very limited research on the topic. However, current studies point towards BU patients being more likely to be infected with HIV, and HIV infection increasing BU severity (174, 175).

IDENTIFYING IMMUNE-METABOLIC HOST THERAPEUTIC TARGETS

Given the significant disease burden of TB and leprosy, the rise in drug resistance and the challenges associated with the development of novel anti-mycobacterial agents, HDT strategies which augment host responses to mycobacterial infections, have become an increasing focus of interest (176–178) (**Figure 3**). Greater understanding of the role of immunometabolism in both protection against, and susceptibility to, infection provides potential targets to promote resistance and modulate tolerance to chronic infection.

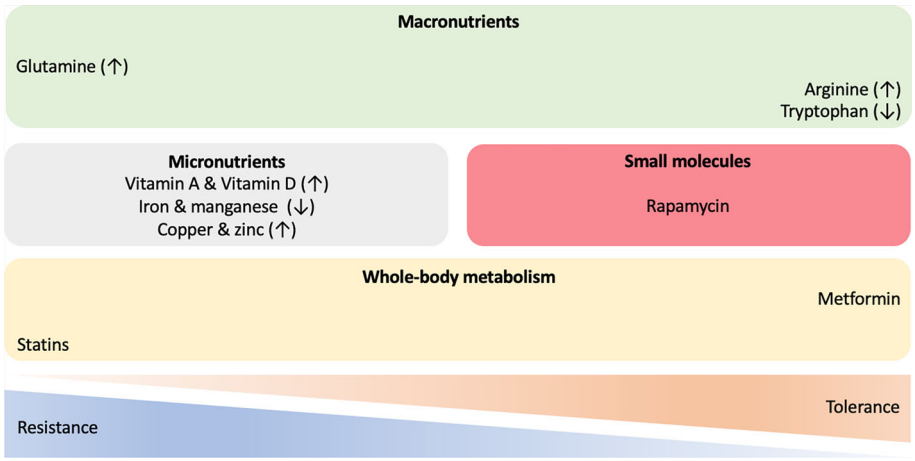

FIGURE 3 | Host-directed therapies in mycobacterial infections. A wide range of approaches and molecules are being investigated to identify novel immune-metabolic targets for treatment of mycobacterial diseases. Therapeutic interventions with macronutrients, micronutrients and small chemical molecules, as well as compounds targeting whole-body metabolism have the potential to shift the resistance/tolerance balance of the host when challenged with mycobacteria. ↑ increased; ↓ decreased.

As discussed, it is well established epidemiologically that individuals with metabolic conditions such as T2D are at increased risk of developing active TB disease, suggesting not only the important role of host metabolic regulation in anti-*M.tb* responses but also pathways for possible therapeutic intervention (179).

In the context of T2D, the antihyperglycemic biguanide drug metformin appears to be a good candidate to modulate mycobacterial tolerance [reviewed in (180)]. Among patients with T2D metformin reduces the risk of *M.tb* infection, the progression to and the severity of TB disease, mortality, lung cavitation, relapse, accelerates sputum conversion and enhances the efficacy of anti-TB drugs (181–186). Several possible mechanisms for the advantageous effects of metformin have been suggested, including enhancing phagocytosis, phagolysosome fusion and autophagy to increase *M.tb* killing in macrophages; the upregulation of mitochondrial ROS production and intracellular antimycobacterial responses; an anti-inflammatory effect to reduce deleterious inflammation (182, 187, 188). Recent work suggests that metformin also educates CD8+ T-cells which results in increased mitochondrial mass, oxidative phosphorylation, and fatty acid oxidation. Such reprogramming of immune-metabolic circuits increases survival capacity and anti-mycobacterial properties of CD8+ T-cells, as seen by enhancement of BCG vaccine protective efficacy and improvements in the sterilizing ability of antibiotics (189). Since butyrate increases susceptibility to TB (134), increasing its concentration by altering gut microbiota might offer another HDT against *M.tb*. Eicosanoids have also been proposed as potential drug candidates for treating TB. In elegant mice experiments, IL-1 induced PGE2 production which promoted *M.tb* control by suppressing type I IFN (85). Furthermore, PGE2 administration resulted in decreased pulmonary *M.tb* load and associated pathology, as well as increased animal survival (85). These promising findings need to be validated in humans and recent evidence highlights the potential of PGE2 as an HDT candidate for treating TB (190). However, a comprehensive understanding of PGE2 kinetics and its effects on the overall immune system will be needed before eicosanoids can be clinically applied (191).

Similar to the action of metformin in targeting whole-body metabolism, statin intake has been associated with significantly reduced risk of developing TB in both T2D patients and non-diabetic general populations (192). Statins reduce inflammation, modulate the immune responses and have direct antimicrobial effects (193). Used as an adjunct, statins enhance the bactericidal activity of first-line TB drugs against intracellular *M.tb* and shortens TB treatment duration (194). Mechanistic studies indicate that statin-mediated reduction in cholesterol levels within phagosomal membranes counteract *M.tb*-induced inhibition of phagosomal maturation and promotes host-induced autophagy, therefore augmenting host responses against *M.tb* (195).

The role of vitamins in host immunity to *M.tb* are of increasing interest. The active form of vitamin A, *all-trans* retinoic acid (ATRA), has been shown to promote autophagy. This results in a reduced bacterial burden in human macrophages infected with *M.tb*, which is induced by cytosolic sensing of double-stranded DNA *via* the STING/TBK1/IRF3 axis (196). Furthermore, ATRA induces a reduction in total cellular cholesterol concentration and promotes lysosomal acidification in *M.tb*-infected monocytes *via* an NPC2-dependent mechanism which results in enhanced antimicrobial activity (197). The possible benefit derived from sunlight and vitamin D supplementation was first suggested in the pre-antibiotic era and has shown to modulate both innate and adaptive immune responses. The biologically active form of vitamin D, 1,25-dihydroxy- vitamin D3 (1,25(OH)2D3), enhances the expression of LL-37 in macrophages, the only cathelicidin-derived antimicrobial peptide found in humans, which promotes the destruction of *M.tb* and consequently autophagy (198, 199). While a series of clinical trials have failed to show vitamin D supplementation impacts on clinical outcomes in TB, there is some

evidence that high-dose vitamin D improves the resolution of inflammatory responses during TB therapy and may be beneficial in a subset of TB patients who have a specific polymorphism in the vitamin D receptor (VDR) (200, 201).

The exploration of possible roles of immunomodulatory macronutrient has, to date, focused on glutamine, arginine and tryptophan. Glutamine pathway genes are differentially expressed in *M.tb*-infected macrophages and in the blood of individuals with LTBI or active TB. Glutamine has been identified as the main nitrogen *M.tb* source within infected macrophages (202). Inhibiting glutaminolysis or reducing the availability of glutamine impairs the production of key cytokines by T-cells (IFNγ, IL-1β, IL-17 and IL-22) in response to challenge with *M.tb*, as does genetic polymorphisms in glutamine metabolism genes (including GLS2, SLC1A5, and SLC7A5) (203). Similarly, L-citrulline and L-arginine are necessary for antimycobacterial responses, mediated by microbicidal NO production *via* inducible NO synthase–mediated L-arginine metabolism in infected macrophages. It has been suggested that targeting this pathway might provide novel approaches for enhancing immunity in mycobacterial disease (204). Interestingly, Arg1 conditional gene-deleted mice presented decreased *M.tb* burden compared to wild types, probably due to enhanced macrophage *M.tb* killing capacities (205). In contrast, L-Arg has been shown to contribute to macrophage *M.tb* clearance (206). Observed differences could be explained by different location of Arg1+ macrophages within the granuloma, as well as their role in different infection stages (207). Finally, tryptophan biosynthesis by mycobacteria under stress conditions has been shown to protect *M.tb* from CD4+ T-cell-mediated killing by IFNγ. Inhibition of *M.tb* tryptophan synthesis by the small-molecule 2-amino-6-fluorobenzoic acid (6-FABA) converts *M.tb* into a tryptophan auxotroph and restores the efficacy of failed CD4+ T-cell-mediated host defence (208). Interestingly, the indole propionic acid (IPA), produced by the gut microbiota, also blocks tryptophan biosynthesis in *M.tb via* inhibition of anthranilate synthase (TrpE) which catalyses the first committed step in the tryptophan biosynthesis pathway, by mimicking the physiological allosteric inhibitor of this enzyme (209). Therefore, in contrast to macronutrient supplementation by glutamine and arginine, tryptophan depletion may have a role in *M.tb* control. In the specific context of macrophages, *M.tb* infection causes indoleamine 2,3-dioxygenase (IDO) upregulation, the first rate-limiting enzyme of tryptophan catabolism (210, 211). This not only decreases tryptophan concentrations, but also produces metabolites which activate the aryl hydrocarbon receptor (AHR), which in turns modulate immune activity. For instance, $Ahr^{-/-}$ mice were unable to control *M.tb* H37Rv infection (212). Excellent recent reviews have further covered the potential intervention of metabolic pathways for HDT against TB (213–216).

Treating infected macrophages with statins reduces the viability of intracellular *M. leprae*, similar to that seen with *M.tb*, raising the possible use of statins as an adjuvant HDT for leprosy (217). Also similar to *M.tb*, autophagy is an exciting possible target for HDT leprosy as it promotes bacterial clearance and antigen presentation (218, 219). Not only does autophagy clear *M. leprae* from macrophages but recent evidence suggests it can modulate leprosy disease presentation, driving paucibacillary tuberculoid leprosy in individuals with more autophagic control with a predominance of IL-26, IFNγ, and TNF, autophagy-inducing cytokines (51, 220–223). Rapamycin, metformin and the antiprotozoal drug nitazoxanide have been proposed as HDTs against leprosy *via* modulating autophagic mechanisms to promote the antimicrobial response against *M.leprae* and decrease inflammation-mediated immunopathology (93).

CONCLUSION

Mycobacterial infections still represent a major public health issue and we need better treatments. A greater understanding of the host-induced metabolic and immune responses to mycobacterial challenge will aid the design of novel, and needed, host-directed therapeutic strategies. Macrophages are mycobacterial targets and constitute a heterogenous cell population; as reflected by their metabolic diversity and plasticity. Mycobacterial infection shapes host cell metabolism and there are clear metabolic and coupled functional phenotypes associated with particular infection outcomes (ie. M1-like favours infection control, while M2-like macrophages are more permissive to infection). Changes in macrophage polarisation upon infection directly impact the concentration of certain intracellular metabolites. They have the potential to post-translationally modify proteins, including histones. Therefore, changes in host cell metabolism can change the epigenetic landscape of the cell, with long term consequences regarding the host ability to control mycobacterial infection (107, 108). Mycobacterial diseases including TB and leprosy do not exist in isolation. Co-morbidities such as smoking, diabetes and HIV infection can worsen TB outcomes, and this can partially be explained by disease-induced metabolic changes. Gaining mechanistic understanding of this phenomenon brings us closer to the design of new and effective therapies, including expanding the use of current drugs such as metformin. There has been outstanding research in the last decades unravelling the links between cell metabolism and induced immune responses. This is a promising avenue that needs pursuing as it holds great potential to identify new targets for therapy that will aid the fight against ancient and devastating epidemics such as TB and leprosy.

AUTHOR CONTRIBUTIONS

AL and CM conceptualised the manuscript. AL, MD, JB, CD, MO'S, and CM wrote the manuscript. All authors contributed to the article and approved the submitted version.

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