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REVIEW

Glucose Metabolic Reprogramming of Macrophages Against *Mycobacterium tuberculosis* Infection

Tianhui Liu[1],*, Zeliang Yang[2],*, Jing Tong[1], Mengqiu Gao[1], Yu Pang[2]

[1]Department of Tuberculosis II, Beijing Chest Hospital, Capital Medical University/Beijing Tuberculosis and Thoracic Tumor Research Institute, Beijing, People's Republic of China; [2]Department of Bacteriology and Immunology, Beijing Chest Hospital, Capital Medical University/Beijing Tuberculosis and Thoracic Tumor Research Institute, Beijing, People's Republic of China

*These authors contributed equally to this work

Correspondence: Mengqiu Gao, Department of Tuberculosis II, Beijing Chest Hospital, Capital Medical University/Beijing Tuberculosis and Thoracic Tumor Research Institute, Beijing, People's Republic of China, Email gaomqwdm@aliyun.com; Yu Pang, Department of Bacteriology and Immunology, Beijing Chest Hospital, Capital Medical University/Beijing Tuberculosis and Thoracic Tumor Research Institute, Beijing, People's Republic of China, Email pangyupound@163.com

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Abstract: Tuberculosis (TB) is a global infectious disease caused by *Mycobacterium tuberculosis* (*Mtb*). Serving as the primary effector cells, macrophages play a crucial role in host immune responses against *Mtb*. During *Mtb* infection, macrophages undergo extensive metabolic reprogramming, notably glycolysis, the pentose phosphate pathway (PPP) and the tricarboxylic acid (TCA) cycle, to adapt to the challenges posed by the pathogen, with glucose metabolic rewiring being particularly critical. This review focuses on the dynamic reprogramming of glucose metabolism in macrophages during *Mtb* infection, highlighting how metabolic adjustments influence the activation state, polarization, and functional capacity of macrophages. Furthermore, we explore the role of glucose metabolic reprogramming in shaping the immune responses against *Mtb*, particularly its contribution to granuloma formation and maintenance. By understanding the intricate interplay between metabolic rewiring and immune function, we discuss the therapeutic potential of targeting glucose metabolic pathways in macrophages as a novel strategy for TB treatment. Overall, this review emphasizes the need for a deeper understanding of the relationship between glucose metabolism reprogramming and the biological function of *Mtb*-infected macrophages and the development of novel immunometabolic therapies—such as metformin (AMPK activator) or PKM2 modulators already used in oncology— to improve the outcomes of TB patients.

Keywords: glucose metabolic reprogramming, macrophages, Mycobacterium tuberculosis

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Introduction

Mtb is the pathogen responsible for TB, primarily transmitted through the respiratory tract via aerosols exhaled by individuals with active pulmonary TB. Despite concerted global efforts, TB persists as a global health emergency, ranking among the top causes of infectious disease mortality according to the World Health Organization (WHO) classifications. In October 2024, the WHO released the *Global Tuberculosis Report 2024*, which estimated that there were 10.8 million incident cases of TB worldwide in 2023, with approximately 1.25 million deaths attributed to the disease.[1] This underscores the urgent need for novel strategies in TB prevention and treatment. Metabolic reprogramming, particularly in immune cells, has emerged as a critical area of research, offering potential insights into enhancing host defense mechanisms and developing innovative therapeutic approaches.

The immunopathogenesis of tuberculosis pivots on the dynamic equilibrium between host defense mechanisms and mycobacterial evasion strategies. *Mtb* infection outcomes are ultimately determined by the host's immunological competence, particularly the efficacy of pathogen clearance through coordinated innate and adaptive immune responses.[2] Macrophages, serving as central orchestrators of antimycobacterial immunity,[3] not only serve as the first line of defense against *Mtb* infection but also deploy a broad antibacterial arsenal—LC3-mediated phagocytosis, metabolic reprogramming, antimicrobial metabolites and peptides, inflammatory factors, and stress granules—while

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integrating upstream IFN-γ/JAK/STAT1, inflammasome and mTOR signals that drive M1/M2 plasticity and regulate the process of antigen presentation.[4] In recent years, the regulatory role of metabolic reprogramming in the function of immune cells has attracted widespread attention. Specifically, glucose metabolic rewiring in macrophages not only influences their polarization state but also directly regulates inflammatory responses through the production of metabolic intermediates that fuel biosynthesis and redox balance.[5] Building on the bioenergetic framework established by O'Neill and Pearce,[6] we here narrow the lens to the Mycobacterium tuberculosis–macrophage axis and update it with post-2016 evidence: (i) itaconate dose-dependently co-targets SDH and TET2;[7] (ii) single-cell sequencing analyses reveal *Mtb*-imposed glycolytic shutdown in human macrophages;[8] and (iii) spatial transcriptomics discloses metabolic zonation within tuberculous granulomas. Together, these findings replace the glycolytic/oxidative binary with a context-specific, spatiotemporal model of TB immunometabolism. However, a clear road map for translating these in-vitro mechanistic insights into measurable patient benefit is still missing. Most studies remain confined to rodent or cell-culture models, and clinical data linking specific metabolic interventions to sputum culture conversion, lung pathology or relapse rates are scarce. Consequently, this review aims to synthesise current knowledge, highlight evidence gaps, and outline how host-directed metabolic modulation could be moved expeditiously from bench to bedside.

The Fundamental Functions of Macrophages

Macrophages are a crucial part of the innate immune system[9] and originate from common myeloid progenitor cells in the bone marrow.[10] They are present in all tissues and act as the primary phagocytic cells.[11] Macrophages help clear cellular debris produced during tissue remodeling and efficiently remove apoptotic cells, thus maintaining immune homeostasis within the body.[10] They are the primary host cells for *Mtb* growth and survival and play a vital role in the host's immune response to *Mtb*.[12] Macrophages exert several essential functions in controlling TB infection, including phagocytosis, the uptake and elimination of pathogens, tissue repair, and the resolution of inflammation.[13,14]

Macrophages, acting as key players in the immune responses, exhibit distinct metabolic signatures that dictate their activation states and functional outputs. Based on the activation status, macrophages are classified into two types, M1 and M2. M1 macrophages are known for their high expression of pro-inflammatory and antimicrobial molecules, such as interleukin-1β (IL-1β), IL-12, and tumor necrosis factor (TNF). These molecules promote the process of inflammation. In contrast, M2 macrophages express higher levels of anti-inflammatory cytokines like IL-4, IL-10, IL-13, and transforming growth factor (TGF-β). These cytokines play important roles in maintaining tissue homeostasis and regulating inflammation.[10,15,16] The metabolic reprogramming of macrophages is a key factor in determining their activation state.[6,17] M1 and M2 macrophages exhibit distinct metabolic profiles that correspond to their functions.[18] M1 macrophages primarily rely on glycolysis for energy production.[16] Although these cells have active pentose phosphate and fatty acid synthesis pathways to provide necessary biosynthetic precursors, the TCA cycle in M1 macrophages is not fully operational, even in the presence of oxygen.[19,20] They can rapidly generate ATP through glycolysis, which is independent of mitochondrial oxidative phosphorylation (OXPHOS). On the other hand, M2 macrophages primarily depend on a fully functional TCA cycle that supports high levels of OXPHOS.[19] This metabolic dichotomy not only fuels distinct functional programs but also shapes the immunological landscape, influencing disease progression and resolution. Understanding the metabolic drivers of macrophage polarization offers a strategic entry point for modulating immune responses in tuberculosis and other inflammatory diseases.

The Role of Glucose Metabolism Reprogramming in Macrophages

Glucose metabolism is essential for macrophage activation, polarization, and pathogen clearance. This metabolic rewiring is not merely a passive adaptation but an active regulatory mechanism that dictates the functional fate of macrophages, enabling them to toggle between inflammatory and resolving states as needed during infection. It involves three pathways: glycolysis, the PPP, and the TCA cycle.

Interferon-γ (IFN-γ) is the physiological cue that commits macrophages to the M1 glycolytic programme.[21] By activating JAK2/STAT1 signalling, IFN-γ up-regulates PFKFB3-driven glycolysis,[22] thereby accelerating glucose flux and reinforcing M1 polarization essential for antimicrobial responses against Mycobacterium tuberculosis.

Glycolysis

The metabolic reprogramming of glycolysis orchestrates a functional shift in macrophages, enhancing the production of pro-inflammatory cytokines through the generation of metabolic intermediates that initiate inflammatory signaling pathways. Hexokinase 1 (HK1), a crucial rate-limiting enzyme in glycolysis, catalyzes the phosphorylation of glucose to glucose-6-phosphate (G6P) when it is bound to mitochondria, thus initiating subsequent glycolytic processes. When HK1 detaches from the mitochondria, G6P is redirected towards the pentose phosphate pathway. This redirection leads to the nitration and inactivation of glyceraldehyde-3-phosphate dehydrogenase (GAPDH) in a manner dependent on inducible nitric oxide synthase (iNOS), subsequently promoting the production of inflammatory cytokines such as IL-6, IL-1β, and TNF-α.[20] Research indicates that Zinc fingers and homeoboxes 2(Zhx2) upregulate the transcription of 6-phosphofructo-2-kinase (PFKFB3) and enhance glycolysis in macrophages.[23] Furthermore, Zhx2 specifically activates glycolysis in a manner dependent on phosphofructokinase-1 (PFK1), thus facilitating the production of pro-inflammatory cytokines. Additionally, pyruvate kinase M2 (PKM2), another key enzyme in the glycolytic pathway, regulates the activation of inflammasomes such as NOD-like receptor family pyrin domain containing 3(NLRP3) and absent in melanoma 2(AIM2) through the phosphorylation of eukaryotic translation initiation factor 2α kinase (eIF2AK2).[24] The activation of these inflammasomes leads to the activation of caspase-1 in cells, resulting in the maturation and secretion of pro-inflammatory cytokines such as IL-1β, IL-18, and HMGB1.[25]

PPP

Macrophages could utilize pathways such as the PPP and mitochondrial succinate oxidation to initiate glucose metabolic reprogramming and promote their inflammatory phenotype.[26,27] The PPP, a branch of glucose metabolism, can process glycolytic products like G6P to generate nicotinamide adenine dinucleotide phosphate (NADPH). NADPH is essential for the survival of macrophages under oxidative stress and inflammatory conditions.[28] Studies have shown that lipopolysaccharide (LPS)-treated macrophages can enhance the classical oxidative burst response through the activation of NADPH oxidase 2 (NOX2).[29] This activation can be inhibited by 2-deoxyglucose (2-DG), which blocks glycolysis. Additionally, inhibiting the PPP with 6-aminonicotinamide (6-AN) suppresses the elevated NOX2 activity induced by LPS and significantly reduces the mRNA expression levels of NOX2 and its organizer protein p47phox.[30] Furthermore, blocking the PPP pathway can decrease the expression of type I interferon (IFN-β) induced by LPS.[30]

The absence of NOX1 and NOX2 could result in a drastic reduction in reactive oxygen species (ROS) production in macrophages. This deficiency impairs the differentiation of monocytes into macrophages and disrupts M2 macrophage polarization. NADPH oxidases (NOXs) play a critical role in inflammatory responses, and NOX1 and NOX2 are particularly important for facilitating the polarization of monocytes into M2 macrophage.[31]

TCA Cycle

When macrophages are stimulated by inflammatory mediators such as LPS and interferon-γ (IFN-γ), they polarize into M1 macrophages, a process closely related to enhanced glycolysis, active TCA cycle, and reduced OXPHOS associated with mitochondrial dysfunction.[32] The TCA cycle can influence the polarization process of macrophages through mechanisms such as metabolic reprogramming, signaling transduction, and regulation of inflammatory cytokine production. During LPS-stimulated M1 macrophage polarization, TCA cycle-associated metabolites, such as citrate, isocitrate, succinate, fumarate, and malate, accumulate in macrophages, while the production of α-ketoglutarate (α-KG) is downregulated.[33,34] In LPS-activated macrophages, the citrate carrier (CIC) exports citrate from mitochondria, further enhancing glycolytic genes through histone acetylation.[35] The inhibition or knockdown of CIC reduces histone H3 lysine 9 acetylation (H3K9ac) at the promoter of glycolytic genes at hypoxia-inducible factor 1α (HIF-1α) binding sites, thereby inhibiting glycolysis.[35] Studies have demonstrated that the TCA cycle product succinate stabilizes HIF-1α, which contributes to the expression of pro-inflammatory cytokine IL-1β.[36]

The Impact of *Mtb* on Glucose Metabolism Reprogramming in Macrophages

After entering the lungs through the oronasal route, *Mtb* first breaches the alveolar barrier to infect host cells. Among these cells, macrophages are the primary targets of this pathogen, and *Mtb* has evolved sophisticated strategies to survive and replicate within these cells, leveraging metabolic reprogramming to create a hospitable intracellular environment.[37] In response to *Mtb* infection, host cells undergo significant metabolic reprogramming, resulting in the differential expression of various cytokines and chemokines associated with the progression and resolution of inflammation.[38,39] During *Mtb* infection, macrophages are activated through epigenetic modifications of genes, alterations in bioenergetic pathways, and differences in cytokine secretion, demonstrating plasticity and adaptability. As described above, macrophage polarization is tightly linked to distinct metabolic programs, with M1 cells favoring glycolysis over mitochondrial respiration. This reliance leads to rapid ATP production by consuming large amounts of glucose, thereby activating the inflammatory response. In contrast, M2 macrophages mainly utilize OXPHOS and fatty acid oxidation (FAO) to generate ATP, thus promoting anti-inflammatory responses and facilitating tissue repair.[40–42] Studies have shown that the intracellular microenvironment of macrophages can be metabolically compatible with the nutritional needs of *Mtb*.[43] When M2 macrophages rely on fatty acid degradation for energy, they also increase the intracellular glucose supply, which provides nutrients that support bacterial survival.[44,45] This intricate metabolic crosstalk underscores the pivotal role of metabolic reprogramming in shaping the host-pathogen interaction and disease progression. As illustrated in Figure 1, *Mtb* infection induces a metabolic shift in macrophages, characterized by the suppression of oxidative

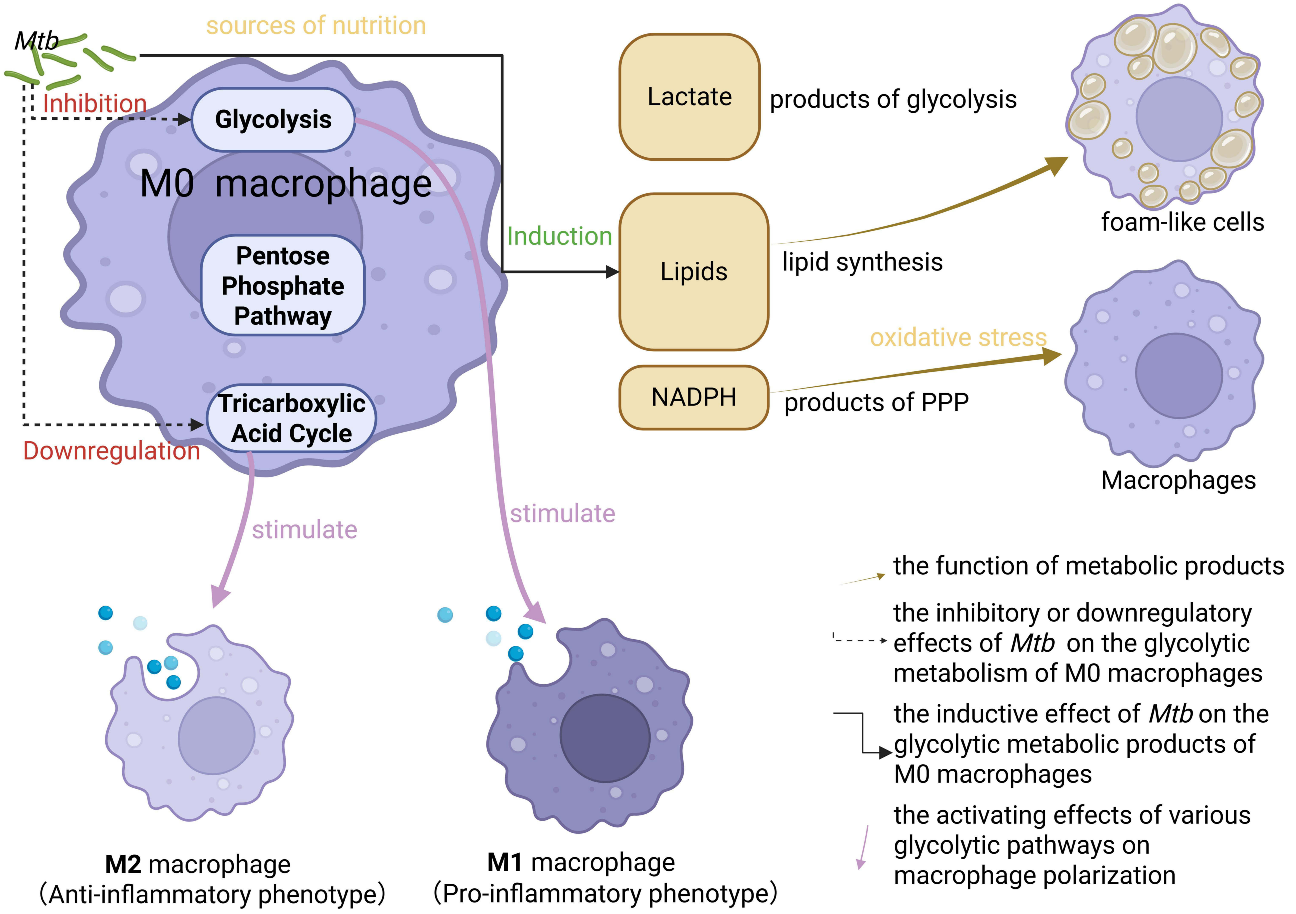

Figure 1 Glucose-metabolic reprogramming orchestrates macrophage fate during Mycobacterium tuberculosis infection.
Note: *Mtb* infection suppresses glycolysis and the TCA cycle in M0 macrophages (naïve macrophages). Glycolysis skews M0 toward M1, whereas the TCA cycle promotes the differentiation of M2. Lactate fuels the bacilli, lipid metabolites promote the formation of foam cells, and PPP-derived NADPH mitigates oxidative stress.

phosphorylation (OXPHOS) and redirection of glycolytic intermediates toward lipid synthesis. This metabolic reprogramming results in lipid accumulation and the formation of foamy macrophages, which provide nutrients such as lactate and lipids that support *Mtb* survival.

As described above, virulent *Mtb* rewires macrophage glucose metabolism toward lipid accumulation and foam-cell formation, thereby supplying the bacilli with lipids and lactate. Additionally, *Mtb* can induce a metabolically inactive state in macrophages by decreasing glycolysis and inhibiting the activity of the TCA cycle.[46] Through upregulating miR-21, *Mtb* targets phosphofructokinase muscle isozyme (PFK-M) in glycolysis, which inhibits the production of pro-inflammatory cytokines, such as IL-1β. This inhibition reduces glycolysis levels and promotes bacterial growth.[47] Salmonella and Listeria likewise rewire macrophage metabolism — suppressing glycolysis and steering substrates to glucose-rich, ROS-poor niches that fuel intracellular replication.[45] *Mtb* exploits a similar strategy but uniquely blocks the Warburg effect, hijacks host lipids for foam-cell formation and assimilates itaconate, underscoring pathogen-specific metabolic nodes amenable to host-directed therapy.

Emerging evidence reveals a distinctive metabolic reprogramming orchestrated by viable *Mtb*, where live pathogens demonstrate selective suppression of macrophage glycolysis-a phenomenon absent in macrophages exposed to heat-inactivated *Mtb* or the attenuated Bacille Calmette-Guérin (BCG) vaccine strain.[46–48] This pathogen-specific metabolic rewiring exemplifies *Mtb*'s evolutionary adaptation to manipulate host cellular metabolism for intracellular persistence. Comparative analyses of infected phagocytes demonstrate striking metabolic divergence: both monocyte-derived macrophages (MDMs) and THP-1 macrophage models infected with virulent *Mtb* exhibit marked attenuation of glycolytic proton efflux rates, whereas BCG-challenged counterparts display paradoxical enhancement of this metabolic parameter.[49] The observed glycolytic suppression in *Mtb*-infected macrophages suggests a sophisticated immune subversion strategy, potentially enabling the pathogen to circumvent antimicrobial host responses through metabolic pathway modulation.

Mounting evidence delineates the metabolic manipulation strategies employed by virulent *Mtb* strains to subvert macrophage antimicrobial functions. Mendonca LE et al established that the pathogenic *Mtb* H37Rv strain selectively inhibits glycolytic flux in both alveolar macrophages (AMs) and bone marrow-derived macrophages (BMDMs), revealing evolutionary specialization of *Mtb* virulence factors in constraining this critical metabolic pathway essential for macrophage bactericidal activity.[50] This metabolic rewiring is not merely a passive adaptation but an active strategy to evade host defenses. Pathogen viability emerges as a critical determinant of metabolic outcomes, as live *Mtb* infection uniquely impedes the bioenergetic transition toward glycolysis and oxidative phosphorylation (OXPHOS), effectively blunting inflammatory effector responses.[51] Comparative analyses reveal a virulence-dependent metabolic reprogramming pattern: THP-1 macrophages exhibit graded increases in glucose uptake proportional to *Mtb* strain pathogenicity, suggesting metabolic adaptation as a hallmark of disease progression.[52] Moreover, increased aerobic glycolysis promotes the activation of apoptotic responses during *Mtb* infection.[53] After infection with H37Rv, M2 macrophages exhibit the greatest metabolic plasticity, becoming metabolically indistinguishable from M1 macrophages. Importantly, the increase in glycolysis in M2 macrophages after H37Rv infection is associated with increased expression of immune response gene 1 (*IRG1*), a key enzyme in itaconate synthesis, which is related to the antimycobacterial capacity of macrophages.[54,55] Studies have shown that during infection with H37Ra (avirulent *Mtb*), 5 mM 2-deoxyglucose (2DG) inhibits glycolysis, resulting in decreased IL-1β (an M1 phenotype marker) and increased IL-10 (an M2 phenotype marker), thereby impairing bacterial killing ability.[38] Although glycolysis can occur in alveolar macrophages infected with attenuated or inactivated forms of *Mtb* in vitro, live virulent *Mtb* eliminates the glycolytic activity of these cells.[47,56]

Mtb infection induces metabolic reprogramming in macrophages, driving them toward the M1 phenotype and enhancing glycolysis to fuel pro-inflammatory responses. However, *Mtb* can exploit bacterial factors, such as the early secreted antigenic target 6 protein (ESAT-6), to manipulate glycolysis excessively, which leads to increased lipid accumulation in macrophages. This accumulation is favorable for the growth of the bacteria.[52] ESAT-6 induces the secretion of interleukin-10 (IL-10) in M1 macrophages, resulting in decreased levels of M1 cytokines such as IL-12 and TNF-α.[57] This shift from the M1 to the M2 macrophage phenotype may be driven by IL-10 production.[58] In addition to IL-10, transforming growth factor-beta (TGF-β) is also produced during mycobacterial infection. TGF-β is associated with TB progression, as shown by a decreased bacterial load in human monocytes infected with the avirulent *Mtb* strain

H37Ra following TGF-β antagonism.[59] The pro-bacterial nature of TGF-β can be attributed to its role in suppressing the effector functions of cytotoxic T cells[60] and promoting macrophage polarization towards the M2 phenotype.[61]

In mice infected with *Mtb*, the glucose metabolism of macrophages undergoes significant changes. In the lung tissue, researchers have observed increased glucose uptake and upregulated glycolysis, as well as enhanced activity of the PPP. Additionally, enzymes involved in the TCA cycle and OXPHOS are downregulated. Further confocal imaging results indicate that these metabolic changes primarily occur in host immune cells, particularly macrophages.[62] During the initial phase of *Mtb* infection, macrophages undergo an inflammatory response, and this shift toward glycolysis may facilitate that process. However, studies have shown that *Mtb* can inhibit glycolysis during later stages of *Mtb* infection, especially by suppressing the production of IL-1β. This suppression helps the bacteria achieve long-term survival within macrophages.[47]

Mtb-Mediated Immune Evasion Strategies Against Host Glucometabolic Reprogramming

Despite the host's metabolic reprogramming aimed at restricting *Mtb* survival, the pathogen has evolved sophisticated strategies to subvert these defenses. *Mtb* actively subverts host innate immune responses through multiple, non-redundant metabolic and signaling interventions. In both murine BMDMs and MDMs, *Mtb* infection significantly upregulates miR-21, which directly targets PFK-M, thereby dampening glycolytic flux, limiting IL-1β production, and facilitating intracellular bacterial survival.[63] Additionally, the *Mtb*-secreted protein Rv2521 directly binds to host NF-κB/p65, preventing its phosphorylation and nuclear translocation. This interference reduces NF-κB/p65 occupancy at the glutathione peroxidase 4 (GPX4) promoter, downregulates GPX4 expression, and induces ferroptosis in macrophages, ultimately promoting bacterial persistence and dissemination.[64] *Mtb* further evades inflammasome-mediated immunity via the serine/threonine protein kinase PknG, which is released into the host cytosol and phosphorylates HOIL-1, a critical component of the linear ubiquitin chain assembly complex (LUBAC). This modification disrupts LUBAC function, impairs NF-κB signaling, and inhibits NLRP3 inflammasome assembly, thereby silencing key innate immune alarms.[65] Moreover, *Mtb* skews macrophage polarization toward an anti-inflammatory M2 phenotype by inducing IL-10 secretion in a STAT3-dependent manner, driving the differentiation of CD14+CD16− monocytes into CD16+CD163+MerTK+pSTAT3+ M2 macrophages with impaired microbicidal activity.[66] Also, *Mtb* sabotages host plasma membrane repair mechanisms by inhibiting prostaglandin E2 (PGE2) biosynthesis, thereby promoting macrophage necrosis and facilitating bacterial egress and reinfection. Collectively, these strategies highlight *Mtb*'s sophisticated ability to reprogram host metabolism, suppress immune signaling, and modulate cell fate to ensure its long-term survival and transmission.[67]

Glycometabolic Products and Host Immune Responses Against *Mtb*

Metabolites produced during the glucose metabolism reprogramming of macrophages play a crucial role in the immune response to *Mtb*. Itaconate is derived from cis-aconitate, which is an intermediate in the tricarboxylic acid cycle, and the enzyme encoded by the *IRG1* catalyzes its production. The formation of itaconate is particularly significant under *Mtb* infection, as it has anti-inflammatory properties. This effect is achieved by inhibiting the activity of succinate dehydrogenase (SDH).[7,68] Additionally, itaconate competes with α-ketoglutarate (α-KG) to inhibit the activity of the DNA dioxygenase TET, which ultimately regulates the expression of inflammatory genes. TET2 is regarded as a key functional target for the anti-inflammatory effects of itaconate.[69] In summary, itaconate can modulate the function of macrophages and influence the host immune response against *Mtb*.

Although itaconate is universally recognized as an immunoregulatory metabolite, its dose–target–function hierarchy is intrinsically multifaceted. Michelucci et al first demonstrated that millimolar itaconate exerts antibacterial activity by inhibiting the microbial enzyme isocitrate lyase.[54] Subsequent studies have revealed that across a low-micromolar-to-millimolar gradient itaconate also competes with succinate to suppress host mitochondrial succinate dehydrogenase[7] and with α-ketoglutarate to antagonize nuclear TET2 dioxygenase,[69] resulting in succinate accumulation and DNA hypermethylation, respectively. These mechanisms converge to down-regulate inflammatory gene transcription. Rather than being mutually exclusive, the prevailing effect is dictated by local concentration, duration of stimulation, and cellular context, underscoring the need for precision layer-specific targeting in future host-directed therapies.

Mesaconate, another metabolite structurally similar to itaconate, also exhibits significant immunomodulatory effects in macrophages. It regulates inflammatory responses by reducing the secretion of pro-inflammatory cytokines such as IL-6 and IL-12 in macrophages stimulated with LPS. At the same time, mesaconate increases the production of CXCL10. While mesaconate has an analogous inhibitory effect on glycolysis compared to itaconate, it has a lesser impact on the activity of the TCA cycle and cellular respiration, and it does not inhibit the activity of SDH. Additionally, mesaconate does not influence the secretion of IL-1β or the activation of inflammasomes, indicating that its immunomodulatory effects are independent of the NRF2 and ATF3 signaling pathways. These characteristics give mesaconate potential therapeutic advantages in anti-inflammatory treatments, particularly because of its minimal impact on cellular metabolism, which could provide a more precise approach to immune intervention.[70]

Lactate plays a critical role in *Mtb* infection through participating in energy production as a metabolite and acting as a signaling molecule that influences immune responses. During *Mtb* infection, low oxygen levels, known as hypoxic conditions, inhibit the activity of prolyl hydroxylase (PHD). This inhibition leads to the accumulation of HIF-1α in the cytoplasm, which then translocates to the nucleus. In the nucleus, HIF-1α dimerizes with the HIF-1β subunit and binds to hypoxia response elements (HRE) in the genome, thus initiating the transcription of various genes, including lactate dehydrogenase A (LDHA). These genes are closely related to the host's adaptation to hypoxia. LDHA catalyzes the conversion of pyruvate to lactate. Lactate can influence the metabolism and function of immune cells by regulating the expression of LDHA and the lactate transporter monocarboxylate transporter-4 (MCT-4),[71] thus affecting the progression of TB. The accumulation of lactate in TB granulomas can impact the polarization, antigen presentation, and inflammatory responses of immune cells, significantly influencing the development of TB. Therefore, lactate and its metabolic pathways may represent potential therapeutic targets for TB. As a major energy source, lactate promotes the acetylation of histone H3K27, allowing the expression of immune-suppressive gene programs, including nuclear receptor subfamily 4 group A member 1 (Nr4a1). This process transcriptionally represses the pro-inflammatory functions of macrophages.[72] Figure 2 summarizes the three major glucose metabolic pathways—glycolysis, the pentose phosphate pathway (PPP), and the TCA cycle—and highlights how their metabolites (eg, itaconate, mesaconate, and lactate) modulate immune responses during *Mtb* infection.

In all, the interaction and regulation among metabolites in the glycometabolism pathway play a crucial role in the immune response to *Mtb* infection, thus influencing TB initiation and progress.

Glycometabolic Architecture of the TB Granuloma

Upon inhalation, *Mtb* first encounters tissue-resident alveolar macrophages (AMs) that rely on fatty acid oxidation (FAO) and oxidative phosphorylation (OXPHOS); this energetically efficient programme limits ROS output and inadvertently provides a lipid-rich replicative niche.[73,74] In contrast, recruited interstitial monocyte-derived macrophages (IMMs) rapidly switch to aerobic glycolysis (the Warburg effect), assume an M1 phenotype and produce TNF-α/IL-1β required for early bacterial containment.[62,75]

As the lesion matures, the granuloma self-partitions into two metabolic zones. In the hypoxic core ($pO_2 < 5$ mmHg), live virulent *Mtb* imposes a "glycolytic brake" by up-regulating host miR-21, down-regulating HK2, PFK-M and PKM2, and diverting glucose-6-phosphate into the pentose-phosphate pathway (PPP); the resulting fall in glycolytic flux and IL-1β output lowers ROS stress and favors bacillary persistence.[60,62,76] Bulk-lung analyses that report Warburg-upregulation[60] reflect the inflammatory rim rather than the metabolically quiescent core, reconciling the apparent contradiction between Shi et al[62] and Cumming et al.[46] At the normoxic rim, FAO-driven OXPHOS sustains M2-like cells that secrete IL-10/TGF-β; while this limits tissue damage, it simultaneously supplies cholesterol and triacylglycerol that *Mtb* sequesters to enter a drug-tolerant, dormant state.[76,77]

Thus, metabolic zonation enables *Mtb* to balance immune evasion with nutrient acquisition. Pharmacological reactivation of core glycolysis (eg, PKM2 activators) combined with FAO inhibition at the rim (etomoxir) converts M2 cells into bactericidal M1 macrophages and accelerates bacterial clearance in murine models,[74,78] validating the granuloma glycometabolic map as a rational framework for host-directed therapy.

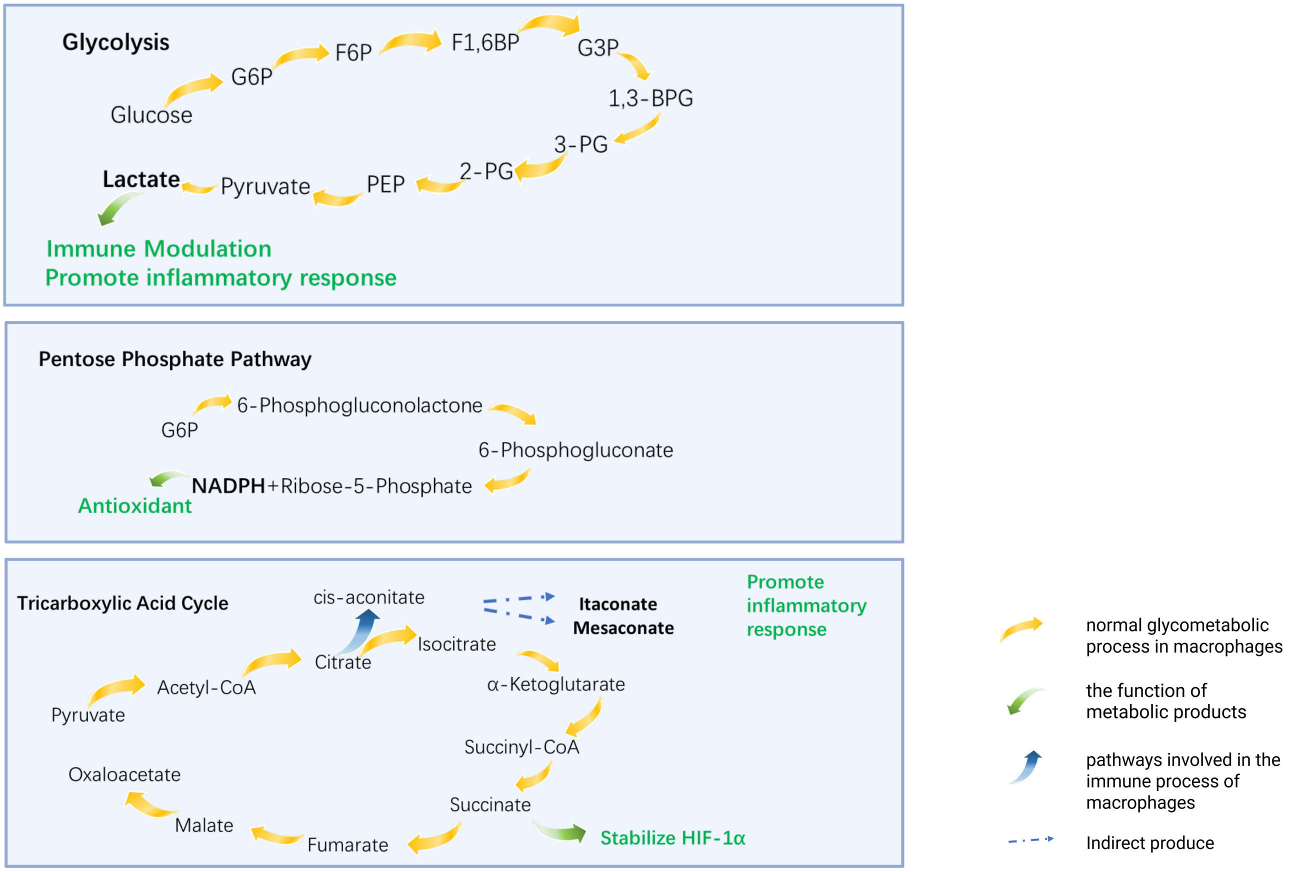

Figure 2 Three glucose metabolic pathways and the effect of their products on immune responses in *Mtb*-infected macrophages.

Therapeutic Strategies Targeting the Glucose Metabolism Reprogramming in Macrophages

The reprogramming of glucose metabolism in macrophages, particularly including the PPP and mitochondrial succinate oxidation, is vital for inflammatory responses.[30] These changes impact both energy production and the synthesis of inflammatory mediators. Understanding how glucose metabolism in macrophages is regulated is essential for developing new therapeutic strategies. For example, shifting the metabolism of macrophages from OXPHOS to glycolysis could enhance the ability to resist infections caused by *Mtb*.[79] When activated by bacterial pathogen-associated molecular patterns (PAMPs) such as LPS, macrophages increase glycolysis and alter mitochondrial metabolism. This results in changes in the TCA cycle and the accumulation of intermediates like succinate and citrate.[80] LPS also raises levels of pyruvate kinase M2 (PKM2), which exists in both dimeric (inactive) and tetrameric (active) forms. PKM2 dimers promote succinate accumulation and drive the transcription of interleukin (IL)-1β,[81] while PKM2 tetramers enhance glycolytic activity. Targeting PKM2's enzymatic activity could offer a potential therapeutic approach.

Nitric oxide (NO), produced by iNOS, plays a crucial role in the glycolytic process of macrophages. Studies have shown that the production of NO is linked to increased glycolysis in these immune cells.[47,79,82] This association may stem not only from enhanced interleukin-1 beta (IL-1β) signaling but also from the production of NADP through the glycolysis-related PPP.[27] NO could form a positive feedback loop with HIF-1α. This interaction not only boosts the activation of macrophages but is also essential for stabilizing HIF-1α. The co-regulation of glycolysis by NO and HIF-1α is critical for macrophages in their function against *Mtb* infection. In macrophages infected with *Mtb* and stimulated by IFN-γ, the absence of NO and HIF-1α results in reduced expression of genes linked to aerobic glycolysis. This reduction impacts glucose uptake and inhibits the aerobic glycolytic process. NO not only directly contributes to the antimicrobial response, but also moderates excessive inflammatory responses by carefully regulating HIF-1α and the glycolysis pathway, thereby protecting host tissues from damage.[82] The increased glycolytic flux in macrophages infected with *Mtb* fosters a pro-inflammatory and antimicrobial environment by modulating inflammation. Additionally, this process deprives the replicating *Mtb* of essential nutrients required for its intracellular growth. Thus, NO may emerge as a significant target in the development of anti-TB immunotherapy.

A study in mice has shown that alveolar macrophages primarily utilize the FAO pathway, which creates a favorable environment for *Mtb*. In contrast, interstitial macrophages exhibit glycolytic activity that can hinder bacterial growth.[83] Additionally, research on BMDMs from mice infected with *Mtb* and treated with 2-DG (a glycolysis inhibitor) or etomoxir (ETO, a FAO inhibitor) has demonstrated that inhibiting glycolysis promotes bacterial growth, while inhibiting FAO can reduce the number of bacteria.[83] Therefore, limiting the activity of alveolar macrophages and increasing the number of interstitial macrophages may be an effective strategy for combating TB.

Iron chelators have been found to influence cell metabolism by regulating HIF-1α. The iron chelator deferoxamine (DFX) can induce IL-1β in human macrophages during the early stages of *Mtb* infection and when stimulated with LPS. Additionally, DFX promotes the expression of key glycolytic enzymes in primary human monocyte-derived macrophages and human alveolar macrophages infected with *Mtb*, thereby enhancing innate immune functions.[84]

Integration with clinical pipelines underscores the translational momentum of these agents. Kim et al listed metformin and the iron chelator deferoxamine (DFX) as priority, clinically safe host-directed candidates.[51] In a phase-II trial of 120 South-African adults, adjunct metformin shortened median time-to-stable sputum culture conversion by 18 days and reduced lung cavity volume on CT versus placebo.[85] Ex-vivo, DFX up-regulates GAPDH and PKM2 transcripts in *Mtb*-infected human alveolar macrophages, confirming enhanced glycolysis;[84] however, DFX has not yet progressed beyond early-phase pharmacokinetic studies. By explicitly aligning bench findings with these evolving clinical read-outs, we provide an up-to-date benchmark for host-directed metabolic therapies.

The chromatin remodeling in innate immune cells stimulated by BCG primarily involves histone modifications, specifically Histone H3 lysine 4 trimethylation (H3K4me3) and Histone H3 lysine 9 trimethylation (H3K9me3), in glycolytic genes. These modifications lead to the activation of the AKT/mTOR/HIF1α pathway, resulting in a metabolic shift in host cells from OXPHOS to aerobic glucose metabolism.[86–88] This research highlights how changes in cell metabolism enhance the production of cytokines, such as TNF-α and IL-6, which are effective in targeting *Mtb*.[89,90]

Macrophages exposed to high glucose levels accumulate increased amounts of oxidized low-density lipoproteins and show reduced capability to control the replication of *Mtb* due to lysosomal dysfunction.[91] Lowering blood glucose levels can improve the host's ability to retard the replication of *Mtb*.[85] Research indicates that metformin, an AMPK activator, can enhance the antimycobacterial functions of macrophages. Metformin inhibits the growth of *Mtb* within host cells in an AMPK-dependent manner. AMPK promotes the expression of peroxisome proliferator-activated receptor γ coactivator 1-α (PGC1-α), which is a crucial enzyme for mitochondrial biogenesis, as well as carnitine palmitoyltransferase 1(CPT1), a key enzyme involved in fatty acid metabolism. Low AMPK expression can negatively impact oxidative phosphorylation metabolism and energy synthesis in cells.[92] AMPK is an energy-sensing kinase, and its activation can significantly influence both cellular metabolism and immune responses. Studies have also shown that metformin can protect cells from inflammation-induced dysfunction in the TCA cycle.[93]

Conclusion

Metabolic reprogramming is central to the host–*Mtb* stand-off because it simultaneously equips macrophages with bactericidal capacity and supplies nutrients or immune-evasion cues to the pathogen. Rapid glycolysis, coupled with the pentose-phosphate pathway, provides ATP, NADPH and anabolic precursors that drive the M1 programme (IL-1β, ROS, NO), whereas oxidative phosphorylation and fatty-acid oxidation typify the M2 state that *Mtb* preferentially exploits. The TCA-cycle-derived metabolite itaconate acts as a rheostat: it inhibits succinate dehydrogenase and limits inflammasome over-activation, yet virulent bacilli can assimilate itaconate and host lipids for carbon and energy. Targeting these nodes offers clinically accessible adjuncts to chemotherapy: (i) metformin or 2-deoxy-glucose can enforce glycolysis; (ii) etomoxir blocks CPT-1-mediated fatty-acid oxidation, curtailing M2 polarization; (iii) the iron chelator deferoxamine stabilises HIF-1α and boosts glycolytic enzymes; and (iv) cell-permeable itaconate derivatives are already used experimentally to limit tissue damage. Several host-directed metabolic interventions are now being tested in early-phase trials: metformin[94] and statins[95] aim to enhance M1 glycolysis and reduce bacterial burden, while deferoxamine is being explored for enhancing the intracellular mycobactericidal activity of certain second-line drugs.[96] However, most studies remain small, open-label or pre-clinical; optimal dosing, pharmacokinetic interactions with anti-TB drugs, and durable endpoints (relapse, lung function) are still undefined. Moreover, patient heterogeneity in diabetes, HIV co-infection and baseline immunity may confound metabolic modulation efficacy. Future large-scale, randomized controlled trials should therefore validate such strategies—alone or combined with existing regimens—to shorten treatment, prevent relapse and reduce lung pathology.

Abbreviations

AIM2, absent in melanoma 2; AM, alveolar macrophages; 6-AN, 6-aminonicotinamide; BCG, Bacille Calmette-Guérin; BMDM, bone marrow-derived macrophages; CIC, citrate carrier; CPT1, carnitine palmitoyltransferase 1; DFX, deferoxamine; 2-DG, 2-deoxyglucose; eIF2AK2, eukaryotic translation initiation factor 2α kinase; ESAT-6, early secreted antigenic target 6 protein; ETO, etomoxir; FAO, fatty acid oxidation; GAPDH, glyceraldehyde-3-phosphate dehydrogenase; G6P, glucose-6-phosphate; H3K27, Histone H3 lysine 27; H3K4me3, Histone H3 lysine 4 trimethylation; H3K9ac, Histone H3 lysine 9 acetylation; H3K9me3, Histone H3 lysine 9 trimethylation; HK1, Hexokinase 1; HIF-1α, hypoxia-inducible factor 1α; HRE, hypoxia response elements; IFN, interferon; iNOS, inducible nitric oxide synthase; IL, interleukin; IMM, interstitial monocyte-derived macrophages; α-KG, α-ketoglutarate; LDHA, lactate dehydrogenase A; LPS, lipopolysaccharide; MCT-4, monocarboxylate transporter-4; *Mtb*, Mycobacterium tuberculosis; NADPH, nicotinamide adenine dinucleotide phosphate; NLRP3, NOD-like receptor family pyrin domain containing 3; NO, Nitric oxide; NOXs, NADPH oxidases; NOX2, NADPH oxidase 2; Nr4A1, Nuclear receptor subfamily 4 group A member; OXPHOS, oxidative phosphorylation; PAMPs, pathogen-associated molecular patterns; PFK1, phosphofructokinase-1; Pfkfb3, 6-phosphofructo-2-kinase; PGC1-α, peroxisome proliferator-activated receptor γ coactivator 1-α; PHD, prolyl hydroxylase; PKM2, pyruvate kinase M2; PPP, pentose phosphate pathway; ROS, reduction in reactive oxygen species; TB, Tuberculosis; TCA, tricarboxylic acid; TGF-β, transforming growth factor; THP-1, Tsuchiya Human Promyelocytic leukemia cell line-1; TNF, tumor necrosis factor; Zhx2, Zinc fingers and homeoboxes 2.

Consent for Publication

All authors have read and approved the final version of the manuscript, attest to the accuracy of its content, and consent to its submission to this journal.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

Tianhui Liu and Zeliang Yang are co-first authors for this study. The authors declare that they have no competing interests in this work.

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