Itaconate, Arginine, and Gamma-Aminobutyric Acid: A Host Metabolite Triad Protective Against Mycobacterial Infection

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Immune metabolic regulation shapes the host-pathogen interaction during infection with Mycobacterium tuberculosis (Mtb), the primary pathogen of human tuberculosis (TB). Several immunometabolites generated by metabolic remodeling in macrophages are implicated in innate immune protection against Mtb infection by fine-tuning defensive pathways. Itaconate, produced by the mitochondrial enzyme immunoresponsive gene 1 (IRG1), has antimicrobial and anti-inflammatory effects, restricting intracellular mycobacterial growth. L-arginine, a component of the urea cycle, is critical for the synthesis of nitric oxide (NO) and is implicated in M1-mediated antimycobacterial responses in myeloid cells. L-citrulline, a by-product of NO production, contributes to host defense and generates L-arginine in myeloid cells. In arginase 1-expressing cells, L-arginine can be converted into ornithine, a polyamine precursor that enhances autophagy and antimicrobial protection against Mtb in Kupffer cells. Gamma-aminobutyric acid (GABA), a metabolite and neurotransmitter, activate autophagy to induce antimycobacterial host defenses. This review discusses the recent updates of the functions of the three metabolites in host protection against mycobacterial infection. Understanding the mechanisms by which these metabolites promote host defense will facilitate the development of novel host-directed therapeutics against Mtb and drug-resistant bacteria.

Keywords: itaconate, arginine, GABA, host defense, Mycobacterium tuberculosis, innate immunity

INTRODUCTION

Metabolites function as innate immune effectors against intracellular bacterial infections, including Mycobacterium tuberculosis (Mtb), the primary pathogen of human tuberculosis (TB). The roles of several metabolites have been determined in host defense against Mtb infection. A significant advance occurred with identifying itaconate, produced by immunoresponsive gene 1 (Irg1) enzymatic activity, in the growth inhibition of mycobacteria possessing isocitrate lyase (1, 2). A recent discovery (3, 4) regarding the anti-inflammatory function of itaconate points to a role in regulating pathological inflammation during Mtb infection. In addition, an earlier study showed that L-arginine (Arg) metabolism is closely related to bacteriostatic activity in macrophages (5).
L-Arg consumption, which is accompanied by nitrite/nitrate production, and L-citrulline exert a fungistatic effect in murine macrophages (5). When produced by arginase-expressing macrophages, L-citrulline activates antimycobacterial responses (6). Ornithine, another metabolite of the L-Arg metabolic pathway, is mainly produced by Kupffer cells in the liver and participates in host defense by activating autophagy (7). Furthermore, γ-aminobutyric acid (GABA), a metabolite and neurotransmitter, activates autophagy to induce innate host defenses against intracellular bacteria, including mycobacteria and salmonella (8).

In recent years, several comprehensive studies have indicated the immunoregulatory functions of these metabolites during host-pathogen interactions in Mtb infection. Here, we focus on the roles and mechanisms by which three metabolites—itaconate, Arg, and GABA—enhance host defenses in macrophages during Mtb infection. Understanding the molecular mechanisms by which metabolites modulate host innate immune pathways will provide therapeutic insight into emerging diseases and human TB.

OVERVIEW OF IMMUNOMETABOLISM IN HOST-MTB INFECTIONS

Macrophages are the principal host phagocytes for Mtb at sites of infection. After phagocytosis by macrophages, Mtb can reside in the phagosomes and circumvent host immune protection by resisting phagolysosomal acidification (9–12). Several macrophage populations are implicated in innate immune defense and infectious pathogenesis, depending on the context (4, 11, 13). Macrophages initiate intracellular innate immune signaling to activate early inflammatory responses following recognition of Mtb and/or its components via specific pattern-recognition receptors (10, 12, 14). Macrophages can be categorized into two major types, i.e., classically activated (M1) and alternatively activated (M2). M1 macrophages exhibit high microbicidal activity and produce proinflammatory cytokines such as tumor necrosis factor (TNF-α) and interleukin (IL)-1β, and inducible nitric oxide synthase (iNOS). By contrast, M2 macrophages participate in tissue repair and produce IL-10, tumor growth factor (TGF)-β, and anti-inflammatory cytokines (15, 16). In addition, macrophages have multiple antimicrobial pathways linking innate immune signaling to various effector mechanisms, including cell-autonomous autophagy pathways. Autophagy activation enhances phagosomal maturation to promote host defense against intracellular mycobacterial infection (10, 12, 17–20). Mtb has multiple strategies for manipulating host innate immune responses and escaping from autophagy to survive inside macrophages (10, 12). A deeper understanding of molecular crosstalks between Mtb and host cells would facilitate the development of new therapeutic strategies against human TB, particularly drug-resistant TB.

Macrophages and other immune cells have distinct metabolic and bioenergetics requirements at different stages of infection (21). Studies involving nonhuman primate TB granulomas showed that M1 polarization is related to a favorable disease outcome (22). During infection, TB granulomas are the active sites of host-Mtb interactions, where Mtb develops mechanisms to resist host protective immunity, and the host localizes the condition (23–26). The alveolar macrophages representing bacterial permissiveness are associated with fatty acid β-oxidation, when compared with glycolytically active interstitial macrophages (27). Metabolic rewiring and epigenetic reprogramming are critical for M. bovis bacillus Calmette-Guérin (BCG)-mediated trained immunity, i.e., long-term immune response to infection or vaccination (28–30). Therefore, the orchestrating immunologic and metabolic responses may determine the outcome of Mtb infection. A general overview of immune metabolic remodeling profiles and the underlying mechanisms are reviewed elsewhere (21, 31, 32) and not discussed here.

ROLE OF ITACONATE DURING MYCOBACTERIAL INFECTION

Conversion of isocitrate to succinate and glyoxylate by isocitrate lyase is the first step in the glyoxylate shunt in several bacteria, including Mtb (33–35), and is involved in Mtb survival during chronic infection (1, 36). Michelacci et al. showed that itaconic acid (also known as methylenesuccinic acid), produced by Irg1, restricts the growth of bacteria harboring isocitrate lyase, such as Mtb and Salmonella enterica (1). In addition, itaconate and itaconyl-CoA target methylcitrate lyase in the methylcitrate cycle and B12-dependent methylmalonyl-CoA mutase, respectively, to restrict bacterial growth (1, 37). However, a recent report demonstrates that the Mtb effector Rv2498c, a bifunctional β-hydroxyacyl-CoA lyase, participates in itaconate dissimilation to confer resistance to itaconate (38). Notably, the MtbΔrv2498c strain shows significantly attenuated virulence in a mouse low-dose aerosol infection model (38). Itaconate also has an immunomodulatory function during infection. Irg1, a mitochondrial enzyme for itaconate synthesis, promotes antimicrobial immune responses against Mtb infection by regulating neutrophil-mediated pathological inflammation during infection (39). Indeed, Irg1 suppresses the production of proinflammatory cytokines and reactive oxygen species (ROS). Significantly, treatment of Irg1−/− bone marrow-derived macrophages with a physiologically relevant dose of itaconate (0.25 mM) shifts the transcriptional patterns toward wild-type macrophages (39). Although Irg1-mediated itaconate production is essential for antimycobacterial responses by regulating excessive pulmonary inflammation, it is unclear how Irg1 regulates inflammatory responses in the context of Mtb infection.

Recently, several studies highlighted using the cell-permeable itaconate derivatives to enhance intracellular delivery. Lampropoulou et al. showed that exogenous dimethyl itaconate at physiological doses markedly inhibits S. typhimurium-induced IL-1β, nitric oxide (NO), but not TNF-α, in macrophages (40). The underlying mechanisms are intriguing because both NO and IL-1β are crucial components of antimycobacterial immune
responses in murine models (41–44). Iaconate treatment also increases the extracellular acidification rate and inhibits succinate dehydrogenase (Sdh), complex II of the mitochondrial electron transport chain, decreasing mitochondrial respiration (40). However, it is unclear whether itaconate-mediated antimycobacterial responses are associated with increased aerobic glycolysis. Moreover, treatment of human primary macrophages with TNF-α and IL-6 suppresses the intracellular growth of M. avium through bystander effects via inducing expression of IRG1 (45). Although the endogenous itaconate level is low, direct delivery of itaconate to M. avium phagosomes may contribute to antimicrobial responses (45) (Figure 1).

To date, the function of itaconate in alveolar macrophages is unclear, although these cells are the first cells that encounter Mtb in the initiation of infection. Future studies are warranted to clarify the role of itaconate in alveolar macrophages during Mtb infection. Recent studies showed that the Irg1 is critically required to control Brucella infection and that dimethyl itaconate has an inhibitory effect against Brucella growth (46). Together, these studies reveal an antimicrobial role for itaconate during bacterial infections, including mycobacteria. However, more studies are warranted to clarify the underlying mechanisms of the itaconate functions of various immune cells, including alveolar macrophages, in mycobacterial diseases.

In an inflammation model, itaconate participates in metabolic remodeling in macrophages toward an anti-inflammatory response by activating nuclear factor erythroid 2–related factor 2 (Nrf2) and inhibiting transcription factor IκB-activating transcription factor 3.

FIGURE 1 | The role of itaconate during mycobacterial infection. Iaconate, produced by immunoresponsive gene 1 (IRG1) from cis-aconitate, modulates TCA cycle by regulating succinate dehydrogenase (SDH, as complex II) activity. Dimethyl itaconate regulates the mRNA expression of inflammatory cytokines in response to LPS. In addition, dimethyl itaconate inhibits NLRP3 and ASC in NLRP3-activating conditions. During Mtb infection, IRG1 and itaconate downregulate inflammatory responses at the transcriptional level and neutrophil recruitment through inhibiting the production of mtROS and inducible nitric oxide synthase (iNOS). In Mtb, itaconate has an antimicrobial activity for methyl citrate lyase (MCL) in the methyl citrate cycle (MCC) and isocitrate lyase (ICL) in glyoxylate shunt, enzymes that are needed for Mtb survival. Moreover, itaconyl-CoA targets B12-dependent methylmalonyl-CoA mutase (MCM-B12) to restrict bacterial growth. Mtb effector Rv2498c participates in itaconate dissimilation to confer resistance to itaconate. During M.avium infection, tumor necrosis factor-α (TNF-α) and interleukin (IL)-6 activate interferon regulatory factor 1 (IRF1)/IRG1 through the autocrine/paracrine signaling pathway. AcCoA, acetyl-coenzyme A; ASC, apoptosis-associated speck-like protein containing a CARD; ATP, adenosine triphosphate; LPS, lipopolysaccharide; M-CoA, methylmalonyl-CoA; MSU, monosodium urate; NLRP3, NLR family pyrin domain containing 3; S-CoA, succinyl-coenzyme A; TLR4, toll-like receptor 4.
inflammatory signaling (47, 48). There are controversial findings upon the function of Nrf2 in the context of mycobacterial infection. Nrf2 is critical for host resistance to pulmonary M. avium complex infection (49, 50); however, it functions in the antioxidant transcriptional responses that delay early Mtb clearance (51). Future studies are needed to address how Nrf2 signaling is associated with itaconate-mediated protection against mycobacterial infection. Moreover, either 4-octyl itaconate or dimethyl itaconate exerts anti-inflammatory effects and inhibits aerobic glycolysis, thus controlling pathologies related to excessive inflammation (4, 46, 52, 53). Therefore these itaconate derivatives may enhance antimycobacterial responses by controlling pathologic inflammation and immunometabolism during infection. More work is needed to define the molecular mechanisms by which endogenous/exogenous itaconate exerts innate host defenses against mycobacterial diseases.

### ROLE OF ARG METABOLISM DURING MYCOBACTERIAL INFECTION

Arg metabolism promotes antimicrobial responses in myeloid cells by inducing NO and regulating inflammatory responses (54, 55). M1 and M2 macrophages catabolize Arg via iNOS and ARG1, respectively. In M1 macrophages, NO synthesis promotes proinflammatory and microbicidal activities against intracellular bacteria (54, 56–58). Although NO plays a critical role in antimycobacterial effect in murine macrophages, its role in human macrophages is still debatable (59). In addition to NO, macrophage anti-Mtb activities induced by L-Arg are dependent, in part, on aerobic glycolysis (60). Moreover, L-Arg synthesis from L-citrulline in myeloid cells contributes to host defense against M. bovis BCG and Mtb H37Rv; deficiency of Ass1 or Asl (to eliminate L-Arg synthesis from L-citrulline) increased mycobacterial growth in macrophages and in vivo (61). In M2 macrophages, ARG1 expression is critical for synthesizing ornithine, proline, and polyamines, and contributes to wound healing, defense against parasites, and humoral immunity (54, 57). ARG1 elimination in macrophages reduces the bacterial load in the lung during Mtb infection (62). Additionally, Mtbc co-infection with helminths such as Schistosoma mansoni increases ARG1 expression in macrophages to aggravate lung inflammation and impair anti-Mtb T cell responses (63). Overall, both iNOS- and ARG1-dependent pathways in Arg metabolism have opposite roles in host defense against Mtb infection. The Arg-citrulline metabolic axis may enhance host control, whereas ARG1-mediated Arg metabolism leads to inadequate antimicrobial responses during intracellular bacterial infection.

A recent study has identified a novel antimicrobial function of ornithine, an amino acid intermediate produced by ARG1 and ARG2 from Arg metabolism and the urea cycle; and also converts to synthesize proline, polyamines, and citrulline (64, 65). Thandi et al. showed that ornithine is involved in antimycobacterial responses in liver macrophages (7). The authors focused on the liver (7) because of its known role in suppressing Mtb infection (66). Kupffer cells in the liver restrict the growth of Mtb more efficiently than other macrophages, including alveolar macrophages, peritoneal macrophages, and bone marrow-derived macrophages (7). Ornithine promotes Kupffer cell-induced inhibition of intracellular Mtb replication by enhancing autophagy and autolysosome accumulation during Mtb infection (7). Mechanistically, AMP-activated protein kinase (AMPK) is required for ornithine-induced antibacterial autophagy in Kupffer cells during Mtb infection (7). In addition to ornithine, Kupffer cells produce imidazole, which does not induce autophagy but exerts an antimicrobial effect on Mtb by inhibiting mycobacterial cytochrome P450 monoxygenases (7) (Figure 2A). However, the mechanism of how ornithine phosphorylates AMPK in Mtb-infected Kupffer cells is unknown. Also, the roles of ornithine and its metabolism at different stages of mycobacterial infection are unclear. Indeed, several types of tumors exhibit increased polyamines, ornithine-related metabolites, leading to transformation and progression (67, 68). In addition, polyamines suppress the intracellular uptake of fluoroquinolones in M. bovis BCG and Mtb, thus causing phenotypic antibiotic resistance (69). A deeper understanding of the comprehensive molecular mechanisms by which ornithine, citrulline, and polyamines regulate host antimicrobial responses against Mtb infection would facilitate the development of novel strategies to boost host immune defense against human TB. Targeting the L-Arg-related metabolic network may enable the development of novel vaccines and host-directed therapeutics against human TB.

In contrast to Kupffer cells, alveolar macrophages fail to clear Mtb and facilitate the establishment of Mtb infection through the upregulation of acetylcholine (7). In addition, alveolar macrophages produce higher ammonia (NH₃/NH₄⁺), promoting Mtb growth, compared with Kupffer cells (7). Interestingly, supplementation of ornithine, imidazole, and atropine (acetylcholine inhibitor) promotes Mtbc clearance in alveolar macrophages (7) (Figure 2B). It is unclear how acetylcholine results in the suppression of Mtbc clearance. Given the recent findings that acetylcholine and cholinergic system favor the progression of mycobacterial infection (70), targeting the non-neuronal cholinergic system in the lungs may contribute to the development of new therapeutics against TB.

### ROLE OF GABA DURING MYCOBACTERIAL INFECTION

GABA is an inhibitory neurotransmitter in the central nervous system and is a metabolite synthesized from glutamic acid by glutamic acid decarboxylase (71–73). Also, GABA is produced in peripheral tissues, including the pancreas, pituitary, testes, gastrointestinal tract, ovaries, placenta, uterus, and adrenal medulla (74, 75). Moreover, peripheral immune cells express GABAergic components—such as type A GABA receptors (GABAₐR), G-protein-coupled type B receptors (GABAₜR), and GABA transporters—which modulate GABA biological functions in peripheral tissues and/or cells (76–79). The peripheral GABAergic system plays an essential role in
autoimmune and inflammatory diseases like type 1 diabetes, experimental autoimmune encephalomyelitis, collagen-induced arthritis, and dermatitis (77, 80, 81).

GABA signaling activates antimicrobial responses against Mtb and M. bovis BCG (8). GABAergic activation via GABA_AR agonists—such as GABA, muscimol, and isoguvacine hydrochloride—induces antibacterial autophagy and phagosomal maturation during Mtb infection. However, GABAergic inhibition suppresses antimicrobial responses during mycobacterial infection. Mechanistically, GABA-induced autophagy activation is mediated by intracellular calcium influx via activation of the AMPK-mediated autophagy pathway and GABA_AR signaling in intestinal epithelial cells to inhibit enterotoxigenic Escherichia coli-induced excessive apoptosis (82). Certainly, AMPK is a crucial metabolic and autophagic regulator and promotes antimicrobial responses against Mtb infection (83–86). However, it is unclear how GABA triggers intracellular calcium influx in peripheral cells to activate AMPK-autophagy pathways. A recent study suggested a molecular framework for GABA-induced Ca^{2+} influx in the context of parasitic infection and immune cell migration (87). In myeloid mononuclear phagocytes such as dendritic cells, glutamate-derived GABA is secreted to trigger GABA_A receptor signaling, implicated in Na–K–Cl cotransporters and extracellular Ca^{2+} influx. The result is phagocyte hypermotility and dissemination of the coccidian parasites Toxoplasma gondii and Neospora caninum (87). Further research is required to identify the role of GABA signaling in different cell types in response to infectious agents.

GABA treatment substantially reduces inflammatory cytokine production in macrophages and lung tissues from infected mice (8). The autocrine or paracrine function of GABA is associated with inhibition of inflammation to ameliorate autoimmune pathologic responses (88, 89). In addition, GABA administration attenuates insulin resistance, obesity-induced adipose tissue macrophage infiltration, and inflammatory responses in subcutaneous inguinal adipose tissues, at least in part via GABA_B receptor signaling (90).

Therefore, GABA signaling pathways can be therapeutic targets for pathologic inflammation during Mtb infection. By contrast, GABA-mediated mammalian target of rapamycin (mTOR) signaling is required for Th17 cell differentiation in the presence of GABA transporter-2 (SLC6A13) deficiency (91). These data suggest a pleiotropic function for GABA in regulating inflammatory responses via downstream signaling molecules.

Mtb co-opts GABA as an immune-escape strategy to favor intracellular infection. Mtb can adapt to acidic conditions and oxidative stresses via the GABA shunt pathway to reduce NAD^{+} and proton levels (92). In addition, Mtb uses lactate and pyruvate from host cells via multiple metabolic pathways, including the GABA shunt (35). Given that GABA promotes host protection against intracellular bacterial infection (8), further research should investigate the molecular mechanisms underlying GABAergic defense in host-pathogen interactions during infection. Pavić et al. revealed that MsGabP, a putative GABA transport protein from M. smegmatis and an Mtb homolog, binds GABA and may outcompete the host GABAergic protective system, providing a
new target for TB drug development (93). A challenging caveat in developing the immunometabolite-targeted host defensive strategies is the complicated host-mycobacterial relationship to compete for the specific metabolites for their purposes during infection. Further studies are needed to understand better how metabolic communication between Mtb and host cells impact disease outcomes during infection.

CONCLUSION

The metabolic interaction between host and mycobacteria is a critical determinant of infection outcomes. However, it is unclear how metabolites and their relationships with other metabolic pathways promote the establishment of chronic infection or control of mycobacteria. In addition, it remains unclear how Mtb manipulates host metabolic fluxes and enzymes to escape immune surveillance and survive intracellularly. The complex interactions between host cells and pathogens via metabolic and immune pathways during Mtb infection will be challenging to unravel.

Itaconate and its derivatives exert bactericidal and immunomodulatory effects critical for antimicrobial defense. Citrulline is a precursor of L-Arg and linked to iNOS-mediated antimycobacterial responses in immune cells; ornithine induces autophagy in Kupffer cells. GABA signaling activates autophagy against intracellular bacteria. Future studies should investigate how these and other immunometabolites influence antimicrobial host defense and pathological inflammation to facilitate a rational design for host-directed therapeutics for mycobacterial infection.

AUTHOR CONTRIBUTIONS

JK wrote the manuscript and made the illustrations. E-JP was responsible for reviewing and editing the manuscript. E-KJ designed, supervised, and wrote the manuscript. All authors contributed to the article and approved the submitted version.

FUNDING

This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIT) (No. 2017R1A5A2015385) and by the National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIT) (No.2019R1A2C1087686).

ACKNOWLEDGMENTS

We are indebted to current and past members of our Medical Research Center (i-MRC) for discussions and investigations that contributed to this article. We apologize to colleagues whose publications could not be cited due to space limitations.
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