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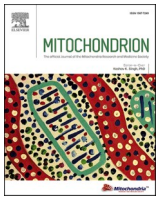

Host and microbial regulation of mitochondrial reactive oxygen species during mycobacterial infections

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ABSTRACT

Mycobacteria, including *Mycobacterium tuberculosis* (Mtb) and non-tuberculous mycobacteria (NTM), pose challenges in treatment due to their increased resistance to antibiotics. Following infection, mycobacteria and their components trigger robust innate and inflammatory immune responses intricately associated with the modulation of mitochondrial functions, including oxidative phosphorylation (OXPHOS) and metabolism. Certainly, mitochondrial reactive oxygen species (mtROS) are an inevitable by-product of OXPHOS and function as a bactericidal weapon; however, an excessive accumulation of mtROS are linked to pathological inflammation and necroptotic cell death during mycobacterial infection. Despite previous studies outlining various host pathways involved in regulating mtROS levels during antimicrobial responses in mycobacterial infection, our understanding of the precise mechanisms orchestrating the fine regulation of this response remains limited. Emerging evidence suggests that mycobacterial proteins play a role in targeting the mitochondria of the host, indicating the potential influence of microbial factors on mitochondrial functions within host cells. In this review, we provide an overview of how both host and Mtb factors influence mtROS generation during infection. A comprehensive study of host and microbial factors that target mtROS will shed light on innovative approaches for effectively managing drug-resistant mycobacterial infections.

1. Introduction

Tuberculosis (TB), caused by *Mycobacterium tuberculosis* (Mtb), is a contagious bacterial infection primarily impacting the lungs but can affect other body parts. Treatment involves prolonged antibiotic therapy, usually lasting six months or more. However, the rise of drug-resistant Mtb strains requires new approaches to TB management (Singh and Chibale, 2021). In addition, non-tuberculous mycobacteria (NTM) refer to mycobacteria other than Mtb and *M. leprae*, and they are ubiquitous in the environment. The global incidence and prevalence of NTM lung disease are escalating and affect both immunocompetent and immunocompromised individuals (Dahl et al., 2022). NTM infections affect both immunocompetent and immunocompromised individuals. Similar to Mtb infection, NTMs possess intrinsic or acquired resistance to conventional antibiotics, emphasizing the need to develop novel strategies to combat NTM virulence and stimulate host defensive mechanisms (Saxena et al., 2021). However, little is known about the precise host defense mechanisms during Mtb and NTM infections.

Reactive oxygen species (ROS) are molecules that are responsible for diverse cellular responses, including mitochondrial respiration, innate immune response, and gene expression. Mitochondria are one of the important organelles that produces ROS and energy in the form of ATP (Sena and Chandel, 2012). Recent studies have unveiled the intricate mechanisms responsible for generating mitochondrial ROS (mtROS), which play a crucial role in triggering host immune responses during mycobacterial infection and inflammation (Lloberas et al., 2020; Tur et al., 2020). While mtROS are crucial for cellular signaling, bactericidal functions, and immune responses, excessive production resulting from mitochondrial dysfunction during infection can cause damage to cellular components such as DNA, proteins, and lipids, thereby leading to immunopathology and necroptotic cell death (Silwal et al., 2020; Weindel et al., 2022). MtROS also play a pivotal role in mediating

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nucleotide-binding and oligomerization domain (NOD)-like receptor (NLR) family pyrin domain (PYD)-containing 3 (NLRP3) inflammasome activation, a key process in inflammation. Additionally, NLRP3 inflammasome-driven inflammation attracts macrophages and neutrophils, triggering their ROS production, thus establishing a feedback loop between ROS and the NLRP3 inflammasome (Liao et al., 2019). Hence, in the context of infectious diseases such as TB and NTM infections, mtROS have been implicated in diverse facets of host-pathogen interactions and contribute to the determination of disease outcomes. However, the mechanisms by which host factors and/or pathways influence the production of mtROS to impact host defense and pathological roles during infection remain unclear. Moreover, several mycobacterial virulence factors are effectively targeted to mitochondria, thereby exerting a significant influence on the intricate functions of these organelles (Guo et al., 2021; Lienard et al., 2020; Sohn et al., 2011). In this review, we present a comprehensive overview of how both host and mycobacterial factors influence mtROS generation during infection. Delving into the dual nature of mtROS, we thoroughly explore its regulation and effects by considering the status of infected macrophages.

2. Host factors/pathways to control mtROS during mycobacterial infection

As key innate immune cells, macrophages act as primary sources of mtROS and cellular ROS in response to invading microbes (Canton et al., 2021). MtROS influence diverse pathways such as metabolism, bactericidal and inflammatory responses, and cell death, thereby playing a dual role, i.e., protective and pathological aspects during mycobacterial infections. In this section, our focus centers on five crucial aspects of host factors: (i) immunometabolic remodeling, (ii) the mitochondrial oxidative phosphorylation (mtOXPHOS) system, (iii) immunometabolites, (iv) the impact of mitochondrial damage, and (v) mitochondrial redox regulation, upon mtROS generation during mycobacterial infections (Fig. 1).

2.1. Immunometabolism and mtROS

Mycobacteria and their components are recognized by numerous pattern-recognition receptors, leading to the initiation of the nuclear factor (NF)-κB-dependent pathway to drive cellular inflammatory responses and the induction of antimicrobial molecules in macrophages (Jo et al., 2007). These innate immune responses are closely intertwined with mitochondrial functional alterations and immunometabolic responses driven by Mtb or NTM bacteria (Lee et al., 2023b; Martin et al., 2023). Importantly, macrophages undergo immunometabolic remodeling depending on their activation status. It is generally believed that during the early stage of infection, macrophages shift into an M1-like phenotype, exhibiting a metabolism characterized by heightened glycolytic flux, increased activity in the pentose phosphate pathway (PPP) and fatty acid biosynthesis, and reduced mitochondrial respiration and impaired tricarboxylic acid (TCA) cycle (Chacon-Salinas et al., 2005). The PPP plays a vital role in NADPH production, essential for ROS and nitric oxide (NO) biosynthesis (Nagy and Haschemi, 2015). In M1 macrophages, the TCA cycle experiences two breakpoints at the citrate and succinate levels, leading to an accumulation of these

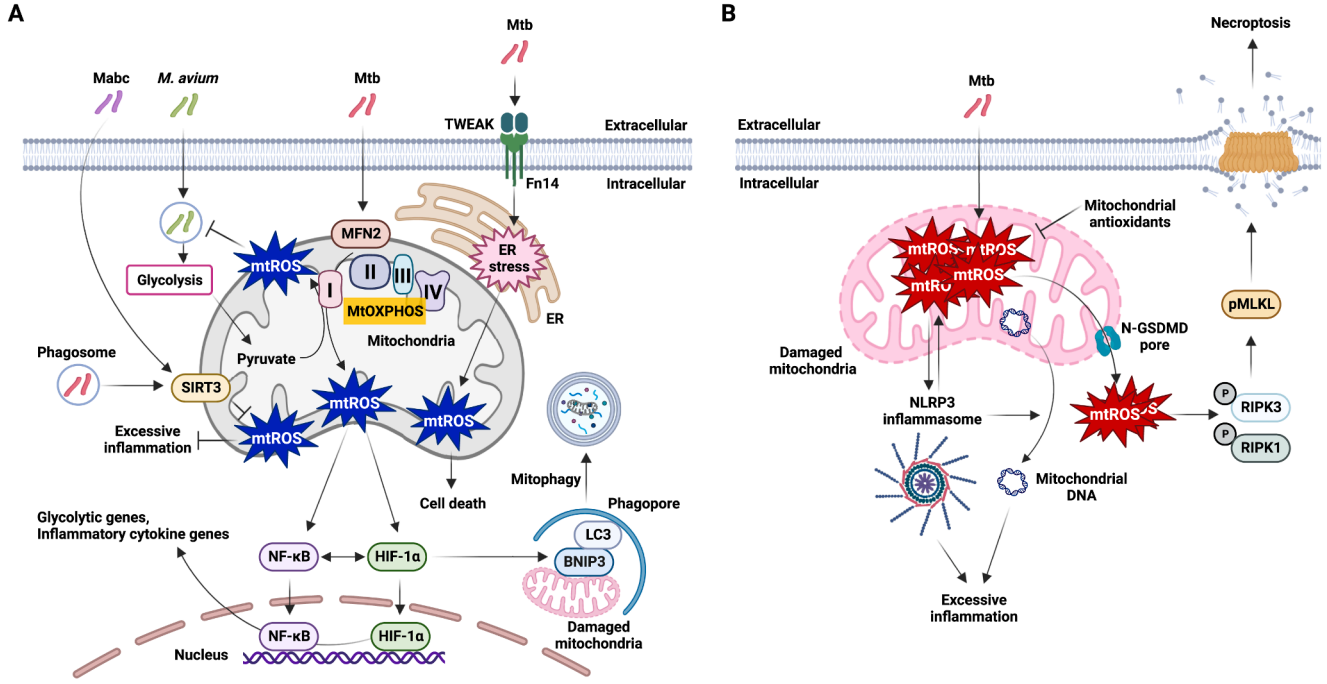

Fig. 1. mtROS-associated host factors/pathways. (A) During mycobacterial infection, mtROS plays two roles. MFN2 produces mtROS through mitochondrial respiratory chain complex I during Mtb infection. The generation of mtROS promotes the expression of glycolytic genes and inflammatory cytokine genes through HIF-1α and NF-κB in macrophages. In addition, mitochondrial pyruvate can produce mtROS, leading to control intracellular survival of *M. avium*. Moreover, Mtb or Mabc infection regulates the expression of SIRT3 and mtROS production to control mycobacterial growth and excess inflammation. In late-stage mycobacterial infection, TWEAK-Fn14 signaling increase oxidative stress to induce ER stress and produce mtROS, resulting in cell death. Mtb infection induces mtROS production and mitophagy through HIF-1α/BNIP3 to remove damaged mitochondria. (B) In disease-associated Lrrk2^{G2019S} macrophages, mitochondrial GSDMD pore can release mtROS from mitochondria and lead to RIPK1/RIPK3/MLKL-dependent necroptosis during Mtb infection. The generation of mtROS activates NLRP3 inflammasome, which in turn can induce further mtROS generation. The activated NLRP3 inflammasome releases mitochondrial DNA from mitochondria to the cytosol, triggering excessive inflammation. BNIP3, BCL2/adenovirus E1B 19 kDa protein-interacting protein 3; ER, endoplasmic reticulum; Fn14, fibroblast growth factor-inducible 14; GSDMD, gasdermin D; HIF-1α, hypoxia-inducible factor 1-alpha; Lrrk2, leucin-rich repeat kinase 2; Mabc, *Mycobacteroides abscessus*; *M. avium*, *Mycobacterium avium*; MFN2, mitofusin 2; MLKL, mixed lineage kinase domain like pseudokinase; Mtb, *Mycobacterium tuberculosis*; mtROS, mitochondrial ROS; mtOXPHOS, mitochondrial OXPHOS; RIPK, receptor-interacting protein kinase; TWEAK, tumor necrosis factor-like weak inducer of apoptosis.

metabolites. Moreover, succinate accumulation stabilizes hypoxia-inducible factor 1-alpha (HIF-1α) by inhibiting prolyl hydroxylases (PHDs), leading to an increased biogenesis of interleukin (IL)-1β (Mills et al., 2016). Both NF-κB and HIF-1α are well-characterized transcription factors that enhance the expression of glycolytic genes (Remels et al., 2015). However, in T cells, HIF-1α also contributes to susceptibility of von Hippel-Lindau factor (VHL)-deficient T cells and its stabilization diminishes CD4 T cell responses during Mtb infection (Liu et al., 2022).

Several studies have highlighted the transcriptional features and their impact on the differentiation of M1 and M2 macrophages during Mtb infection (Roy et al., 2018). Roy et al. demonstrated that the expression of unique genes and long non-coding RNAs depends on the macrophage phenotypes following Mtb infection (Roy et al., 2018). During Mtb infection, the gene expression and metabolic processes of both Mtb itself and host cells are largely altered. Utilizing transcriptional profiles, Rohde et al. previously reported that Mtb regulates its gene expression and metabolism during intracellular adaptation in macrophages. Up to day 2, genes involved in stress responses undergo changed; however, genes associated with fatty acid and cholesterol metabolism are altered to utilize host-derived cholesterol and fatty acids (Rohde et al., 2012). Furthermore, a previous study showed that in the absence of both type I and type II interferon (IFN) receptor signaling, the classically activated macrophage phenotype (M1) can be switched to the alternatively activated macrophages phenotype (M2) towards a more permissive status and increased bacterial burden during Mtb infection *in vivo* (Moreira-Teixeira et al., 2016).

On the host side, mitofusin (MFN)-2, a mitochondrial fusion protein, plays a crucial role in maintaining aerobic glycolysis by inducing HIF-1α during mycobacterial infection (Silwal et al., 2021). Notably, MFN2′s action in sustaining HIF-1α and proinflammatory responses is linked to the activation of the mitochondrial respiratory chain complex I and mtROS production in macrophages (Silwal et al., 2021). Therefore, the components of mitochondrial dynamics likely play a critical function in the generation of mtROS, promoting aerobic glycolysis and inflammatory responses that favor antimicrobial actions against mycobacteria.

Thus, Mtb-induced metabolic rewiring of host cells contributes to the persistence of Mtb, while several host factors influence mitochondrial function and metabolic shifts to counteract mycobacterial strategies during infection. More comprehensive studies on the interrelationship between host and mycobacterial crosstalk upon metabolic reprogramming will facilitate the future development of new therapeutics against Mtb infection.

2.2. MtOXPHOS system intertwined with immune functions

The persistent nature of inflammatory responses can have detrimental effects on the host. As inflammation progresses, macrophages undergo an immunometabolic shift towards mitochondrial metabolism, resulting in increased mtOXPHOS. Similarly, M2-like macrophages exhibit upregulated OXPHOS, heightened activity in the TCA cycle, and enhanced glutamine metabolism to support M2 activation (Liu et al., 2021). During OXPHOS, mitochondria utilize oxygen to produce ATP, simultaneously generating mtROS as byproducts (Shadel and Horvath, 2015). The electron transport chain (ETC) consists of electron transports bounded to the inner mitochondrial membrane (IMM), creating a proton gradient across the mitochondrial membrane from the mitochondrial matrix into the intermembrane space. This gradient contains the energy required for ATP synthesis. Complex V enables H^+ ions to re-enter the mitochondrial matrix, harnessing the energy necessary for synthesizing ATP from adenosine and phosphate (Cadonic et al., 2016). During this process, electrons move through the ETC and ultimately reach complex IV, where they combine with molecular oxygen (Nolfi-Donegan et al., 2020). The respiratory chain complexes I, III, and IV, all of which are considered the main producers of mtROS in the form of superoxide anion, represent the most critical and potentially hazardous form of mtROS (Iwasaki et al., 2020; Lambert and Brand, 2004).

Recent studies indicate the immune regulatory functions of each complex in the mitochondrial ETC. Complex I is responsible for generating mtROS, playing crucial roles in inflammatory macrophages and Th17 cells. Complex II facilitates reverse electron transport in macrophages and regulates fumarate levels linked to epigenetic changes. Complex III produces mtROS activating HIF-1α and affecting regulatory T cell function. Complex IV is essential for T cell activation and differentiation, while Complex V supports Th17 differentiation and interacts with anti-tumor T and natural killer (NK) cells (Yin and O'Neill, 2021). In the context of mycobacterial infections, several reports present conflicting perspectives on the roles of mtOXPHOS concerning host defensive responses. Mtb infection downregulates the expression of mtOXPHOS-related proteins and enzymes in mouse lungs in the early stage. However, there is elevated aerobic glycolysis, i.e., the Warburg effect, similar to the metabolic signature of cancer cells (Shi et al., 2015). It has been reported that the shift from mtOXPHOS to glycolysis, mediated by HIF-1α, is crucial for the microbicidal activity against Mtb infection (Marin Franco et al., 2020). When M1 macrophages were exposed to the fluids of tuberculous pleural effusions, the eicosanoid fraction of tuberculous pleural effusion fluids reduces glycolysis and increases mtOXPHOS and bacillary load (Marin Franco et al., 2020).

On the other hand, a recent study highlights mtOXPHOS-mediated protective innate memory induced by activating M2 macrophages with IL-4 and IL-13 during mycobacterial challenge (Lundahl et al., 2022). Both human and murine models demonstrated that prior IL-4/13 activation leads to increased pro-inflammatory cytokine secretion upon secondary mycobacterial stimulation, accompanied by enhanced killing capacity. Interestingly, IL-4/13-trained macrophages maintain elevated mtOXPHOS, which is crucial for sustaining pro-inflammatory responses (Lundahl et al., 2022). This oxidative stress may contribute to proinflammatory responses and resistance to Mtb infection. These findings indicate that Mtb downregulates mtOXPHOS in host cells during the early stage of infection. Moreover, the roles of mtOXPHOS may vary based on the macrophage activation status within the broader context of the infection progression.

2.3. Immunometabolites impacting mtROS

Itaconate, by product of the remodeled TCA cycle, plays a critical role in eliciting anti-mycobacterial responses and suppressing inflammatory reactions in M1 macrophages (Kim et al., 2022). Remarkably, itaconate and its derivatives, such as 4-octyl itaconate, exhibit potent activity in scavenging ROS and reducing inflammation (Chen et al., 2022a). In the context of mycobacterial infection, the itaconate derivative, dimethyl itaconate, does not directly exhibit bactericidal activity. However, it triggers antimicrobial responses against Mtb and NTM infections, including multidrug-resistant bacteria, through multifaceted activation of innate immune pathways, including autophagy (Kim et al., 2023). Nevertheless, it remains unclear whether itaconate's antimycobacterial action is mediated by modulating mtROS generation during infection. Additionally, iron can impact cellular metabolism, and iron chelation leads to a dysfunctional ETC, resulting in decreased ROS production (Phelan et al., 2018). For pathogenic mycobacteria, iron is a vital cofactor, and their survival and virulence depend on iron availability (De Voss et al., 1999). Kotey et al. reported that intracellular iron accumulation enhances the survival of *M. avium* in mouse bone marrow-derived macrophages (Kotey et al., 2023). During Mtb infection, heparin treatment increases the expression of ferroportin, the iron exporter protein; thus, intracellular Mtb decreases the iron availability in human macrophages (Abreu et al., 2018).

In mitochondria, nicotinamide adenine dinucleotide (NAD^+) is reduced to nicotinamide adenine dinucleotide hydride (NADH) to produce ATP (Cortassa et al., 2019). During Mtb infection, the tuberculosis necrotizing toxin (TNT), a NAD^+ glycohydrolase, induces NAD^+ depletion and necroptosis through receptor-interacting protein kinas 3

(RIPK3)/mixed-lineage kinase domain-like (MLKL) in macrophages (Pajuelo et al., 2018). Additionally, TNT triggers the production of mtROS, leading to the activation of necroptosis (Pajuelo et al., 2018). However, mtROS generation can be induced by NAD^+ depletion itself independent of TNT (Pajuelo et al., 2020). Furthermore, in human macrophages, mitochondrial pyruvate import enhances the production of mtROS, effectively controlling *M. avium* infection. Importantly, pyruvate import induces mitochondrial hyperpolarization and increased mtROS production by complex I, promoting antimicrobial responses during infection (Rost et al., 2022). These findings robust support the idea that immunometabolites, capable of modulating mtROS generation, hold promise as effective adjunct treatments for hard-to-treat mycobacterial infections in various contexts.

2.4. Mitochondrial damage and mtROS in infection pathology

Mitochondrial dysfunction plays a significant role in the activation of the NLRP3 inflammasome, a critical protein complex involved in immune responses. This activation is triggered by the release of harmful substances such as mtROS and mitochondrial DNA (mtDNA) (Carlos et al., 2017; Wu et al., 2013). Importantly, a robust production of ROS is induced by inhibiting mitochondrial complexes I and II, while blocking the mitochondrial VDAC suppresses the generation of ROS and inflammasome activation (Li et al., 2021). Additionally, the altered integrity of the mitochondria-associated membrane (MAM) sets off a complex cascade of events, including ROS generation, mitochondrial damage, and inflammatory responses mediated by the NLRP3 inflammasome complex (Pereira et al., 2022; Zhao et al., 2019). In the context of *M. bovis* infection, endoplasmic reticulum (ER) stress activates the NLRP3 inflammasome and mature IL-1β production through mtROS generation, while absent in melanoma 2 (AIM2) triggers mitochondrial damage (Liao et al., 2019). Another study showed that *M. bovis*-induced AIM2 inflammasome activation does not depend on ROS or IFN-β release (Yang et al., 2013).

Mitophagy, a selective form of autophagy, is triggered by mitochondrial stress, including mitochondrial damage and hypoxia. In BCL2/adenovirus E1B 19 kDa protein-interacting protein 3 (BNIP3), one of mitophagy receptors, knock-out macrophages show decreased Mtb-induced mitophagy. This mitophagy inhibition results in the accumulation of mtROS and the induction of antimicrobial responses during Mtb infection (Lee et al., 2023a). Additionally, MFN2 is involved in the generation of mtROS, while MFN2 does not impact mitophagy during Mtb infection (Silwal et al., 2021).

Several host factors and pathways play vital roles in controlling mtROS production during host defense against mycobacterial infections. In the late-stage mycobacterial infection, persistent TWEAK-Fn14 signaling disrupts the mitochondrial membrane potential in macrophages, causing mtROS accumulation and activating cell death-related proteins (Chen et al., 2022b). In disease-associated $Lrrk2^{G2019S}$ macrophages, inflammasome activation with increased mtROS triggers gasdermin D (GSDMD) pores on mitochondrial membranes, leading to RIPK1/RIPK3/MLKL-dependent necroptosis and severe immunopathology during Mtb infection (Weindel et al., 2022). Moreover, sirtuin 3 (SIRT3), an NAD^+-dependent protein deacetylase, is downregulated during Mtb infection, leading to increased ROS, mitochondrial stress, and macrophage cell death. In SIRT3-deficient mice, bacterial burden and immune pathology worsened, highlighting SIRT3′s role in mediating host defense during Mtb infection (Smulan et al., 2021). Additionally, during *Mycobacteroides abscessus* (Mabc) infection, the loss of SIRT3 elevates bacterial loads, histopathological damage, and inflammation. Reducing mtROS lessens Mabc burden and inflammation, while inducing SIRT3 expression in infected lungs (Kim et al., 2020). Mtb infection induces mitochondrial damage and the production of mtROS, and these changes are more severe in Sirt3-decifient macrophages (Kim et al., 2019). In other words, SIRT3 is required for the maintenance of mitochondrial homeostasis and protection from stress conditions. However, further investigation is needed to elucidate the precise mechanism by which SIRT3 regulates mitochondrial homeostasis during mycobacterial infection. Furthermore, mitochondrial morphological changes can also contribute to the generation of mtROS during mycobacterial infection. Mtb infection increases mitochondrial fragmentation, and the expression of mitochondrial fission and fusion proteins is altered in macrophages (Lee et al., 2019). In MFN2-deficient macrophages, the expression of mitochondrial respiratory complex I is reduced; however, mitochondrial fragmentation and intracellular survival of Mtb are increased (Silwal et al., 2021). A deeper understanding of host factors that modulate mtROS in disease contexts will aid in developing new strategies to manage TB and NTM infections.

2.5. Mitochondrial redox regulation to control mtROS during infection

Given that excessive mtROS production can instigate mitochondrial dysfunction and oxidative stress, it is crucial to regulate the mitochondrial antioxidant system. Specifically, the dysregulation of mitochondrial redox homeostasis induces oxidation proteins, membrane, and lipids within cells, ultimately leading cell death (Huang et al., 2019). Treatment with the mitochondrial antioxidant MitoTEMPO or NecroX inhibits proinflammatory cytokine production in Mtb-infected macrophages (Kim et al., 2019). Furthermore, the mtROS inhibitor MitoQ reduces the production of IFN-β during H37Rv/Lineage 4 and 4334/Lineage 2 infections but has no effect on the intracellular survival of Mtb (Wiens and Ernst, 2016). Chenling et al. also demonstrate that MitoQ treatment reduces Rv0928-overexpressing *M. smegmatis*-induced proinflammatory cytokines production, including IL-6, tumor necrosis factor-α, and monocyte chemoattractant protein-1, in RAW264.7 cells (Xu et al., 2023). In $Sirt3^{-/-}$ macrophages, MitoTEMPO treatment results in a partially decreased accumulation of mtROS, thereby restoring cellular viability and contributing to mitochondrial redox regulation and cell death during Mtb infection (Smulan et al., 2021). These findings suggest that mitochondrial-targeted antioxidants may serve as a therapeutic target by regulating the production of mtROS against mycobacterial infection.

3. Mycobacterial effectors to control mtROS during infection

Recent studies have shed light on the role of mycobacterial effectors in influencing mitochondrial functions and mtROS generation during infection. This research underscores the significance of microbial effectors in evading host defense mechanisms, ultimately impacting infection outcomes. This session focuses on mycobacterial effectors that target mitochondria and modulate ROS production, influencing host protective and pathological responses depending on the context (Table 1).

In a recent study, EspC, a substrate protein of the ESAT-6 secretion system (ESX-1), was found to induce ER stress, leading to proinflammatory cytokine production and ROS accumulation. Overexpression of EspC in *M. smegmatis* resulted in increased bacterial survival, accelerated mouse mortality, and ER stress-induced apoptosis, highlighting its crucial role in Mtb spreading and pathogenesis during infection (Guo et al., 2021). Additionally, intact ESX-1 function was found to be crucial for type I IFN production, correlating with the release of mitochondrial and nuclear host DNA into the cytosol (Lienard et al., 2020). Moreover, a recent cryo-EM study demonstrated that Mtb EspB, a component of the type VII secretion system, possesses a mitochondrial membrane-binding property. It interacts with phosphatidic acid and phosphatidylserine in host cell membranes, potentially stabilizing the C-terminal domain in the presence of phosphatidic acid (Sengupta et al., 2023). These findings offer strong evidence that mycobacterial ESX proteins play a vital role in targeting and interacting with host mitochondrial components during mycobacterial infections.

Another recent study revealed that Mtb PtpA interacts with the human trifunctional protein enzyme (hTFP), a crucial mitochondrial

Table 1
Mycobacterial effectors targeting mitochondria during infection. BAL, bronchoalveolar lavage; BMDMs, bone marrow-derived macrophages; *E. coli*, *Escherichia coli*; ETC, electron transport chain; HBHA, heparin-binding hemagglutinin; hTFP, human trifunctional protein enzyme; *M. leprae*, *Mycobacterium leprae*; *M. marinum*, *Mycobacterium marinum*; MMP, mitochondrial membrane potential; MOM, mitochondrial outer membrane; MOMP, mitochondrial outer membrane permeabilization; Mtb, *Mycobacterium tuberculosis*; mtROS, mitochondrial reactive oxygen species; OXPHOS, oxidative phosphorylation; PGL-1, phenolic glycolipid 1; PHB2, protein prohibitin 2; TNT, tuberculosis necrotizing toxin.

Mycobacterial effectors	Effects on mitochondria	Outcome	Model	Ref.
Mycobacterium tuberculosis				
EspC	Mitochondrial transmembrane potential dissipation, MOMP	ER stress-mediated apoptosis, Increased bacterial survival	RAW264.7 cell line	(Guo et al., 2021)
EspB	Interaction with MOM	Host-Mtb interaction	Overexpression in *E. coli* BL21 (DE3) cells	(Sengupta et al., 2023)
PtpA	Decreased mitochondrial localization of h*TFP*α	Dephosphorylation of TFP	Transformed *E. coli* BL21 (DE3)	(Margenat et al., 2023)
Cpn60.2	Interaction with mitochondrial mortalin	Anti-apoptotic effect	THP-1 cells, RAW264.7 cell line	(Joseph et al., 2017)
RipA	Mitochondrial localization	Activation of NF-κB ignalling, Inhibition of autophagy, Decreased ETC enzymes, Inhibition of caspase-dependent apoptosis	RAW264.7 cell line, HEK293T cell line	(Shariq et al., 2021)
HBHA	Mitochondrial damage	Apoptosis, ROS production	RAW264.7 cell line, A549 cell line	(Sohn et al., 2011)
PE_PGRS30	Mitochondrial dysfunction	Reduction of PHB2 in mitochondria, Cellular apoptosis	RAW264.7 cell line, BAL cells	(Matsumura et al., 2023)
C-terminal of PE6/Rv0335c protein	Depolarization of MMP	Increased intracellular ratio of ADP/ATP, Increased the intracellular Ca^{2+} influx, Enhanced caspase-mediated apoptotic cell death	THP-1 cells	(Medha et al., 2023)
Rv0674	Regulation of OXPHOS, Increased mtROS production	Increased apoptosis, Promotion the intracellular survival of mycobacteria	J774A.1 macrophages	(Dubey et al., 2021)
TNT	Mitochondrial damage, Increased mtROS production	Induction of necroptosis, Increased mycobacterial replication	THP-1 cells, Jurkat 655-TNT cell line	(Pajuelo et al., 2020)
Mycobacterium marinum				
Intact ESX-1	Mitochondrial DNA release	Nuclear DNA release, Induction of type I IFN response	BMDMs	(Lienard et al., 2020)
Mycobacterium leprae				
PGL-1	Mitochondrial damage	Increased reactive nitrogen species damages	Zebrafish larvae	(Madigan et al., 2017)

enzyme involved in fatty acid β-oxidation. Notably, PtpA targets and dephosphorylates a specific residue, Tyr-271, on hTFPα, affecting its subcellular localization and activity (Margenat et al., 2023). As mentioned above, TNT, a major cytotoxic factor of Mtb, induces macrophage necroptosis via NAD^+ hydrolysis, increasing mtROS, cell death, and mycobacterial replication (Pajuelo et al., 2020). During *M. leprae* infection, the nerve damage response is triggered by phenolic glycolipid 1 (PGL-1), which prompts the production of nitric oxide synthase, elevated reactive nitrogen species that harm axons by affecting mitochondria and causing demyelination (Madigan et al., 2017). Additionally, Cpn60.2, an abundant Mtb chaperone protein essential for bacterial growth, exhibits the ability to translocate to mitochondria and interact with host mortalin, an HSP 70 gene family member crucial in apoptosis modulation. This interaction leads to a robust anti-apoptotic effect, effectively promoting Mtb survival within the hostile macrophage environment (Joseph et al., 2017). Moreover, Mtb RipA (Rv1477), a peptidoglycan hydrolase, activates NF-κB signaling, leading to the induction of pro-inflammatory cytokines via toll-like receptor 4. RipA localizes in mitochondria, hindering mtOXPHOS enzyme production, while promoting a Warburg-like phenotype that favors bacterial replication. Additionally, RipA inhibits caspase-dependent cell death, impairing innate antibacterial responses (Shariq et al., 2021). These findings highlight how several Mtb proteins create a permissive replication niche within host cells by modulating mitochondrial functions.

Mycobacterial heparin-binding hemagglutinin (HBHA) triggers macrophage apoptosis by inducing ROS production and Bax activation (Sohn et al., 2011). Although HBHA-induced ROS generation may not be exclusively derived from mitochondria, the potent ROS inhibitor N-acetylcysteine effectively mitigates HBHA-induced apoptosis. Interestingly, the HBHA protein specifically targets the mitochondrial compartment, resulting in the dissipation of the mitochondrial transmembrane potential (ΔΨ(m)) and depletion of cytochrome *c* in both HBHA-treated and Mtb-infected macrophages (Sohn et al., 2011). In addition, Mtb PE_PGRS30, an apoptosis-inducing protein, interacts with prohibitin 2 (PHB2) through their respective domains: PGRS (polymorphic GC-rich sequence) and the mitochondrial targeting sequence. Overexpressing PHB2 reduces macrophage apoptosis triggered by PE_PGRS30. However, the PGRS domain of Mtb PE_PGRS30 disrupts PHB2′s ability to maintain mitochondrial structure, resulting in mitochondrial dysfunction and cellular apoptosis (Matsumura et al., 2023). Another study (Medha et al., 2023) demonstrated that the distinctive C-terminal of Mtb PE6/Rv0335c protein plays a role in inducing host mitochondrial perturbations and caspase-mediated apoptosis in macrophages. Interestingly, Mtb Rv0674 (MS_Rv0674) is also involved in the host apoptosis through interaction with the mitochondrial DNA control region, increasing mRNA expression in mtOXPHOS subunits, to influence ATP synthesis, mitochondrial membrane potential, and superoxide production (Dubey et al., 2021). These findings collectively suggest that a variety of mycobacterial proteins play roles in modulating mitochondria, contributing to the establishment of infection pathogenesis during the infection.

4. Conclusions

Mounting evidence acknowledges the dual role of mtROS in infection and inflammation, exhibiting both antimicrobial and pathological effects. However, the precise regulatory mechanisms governing mtROS production remain elusive. Recent research indicates the involvement of

various host factors, such as immunometabolic remodeling, several immunometabolites, and the mtOXPHOS system, in the generation of mtROS. Notably, certain mitochondrial components like MFN2 and SIRT3 play a critical role in preventing mitochondrial damage while simultaneously inducing mtROS to enhance antimicrobial functions. These factors and pathways influence the delicate balance between protective and pathological responses during mycobacterial infections. Indeed, mitochondrial damage followed by mtROS generation contributes to excessive inflammation and necroptotic cell death during mycobacterial infections.

A recent discovery has challenged the prevailing notion that several mycobacterial proteins can target mitochondria and interact with host mitochondrial components during infections. These mycobacterial proteins exert control over immunometabolism, mitochondrial functions, innate immune responses, inflammation, and cell death, thereby evading the host's defense mechanisms during infections. Further research is crucial to unravel the host and microbial factors involved in modulating mtROS, which plays a critical role in innate immune defense mechanisms. Presently, researchers are exploring interventions that target mtROS in TB to gain precise insights into its role in disease progression and outcome. This comprehensive understanding will open avenues for innovative therapeutic approaches. Potential interventions may include regulating mtROS production, modulating the host immune response, or enhancing cellular antioxidant defense systems. The ultimate objective is to uncover novel strategies for managing TB, leading to improved treatment outcomes and potentially overcoming drug resistance.

CRediT authorship contribution statement

Jin Kyung Kim: Review and editing, Visualization. **Eun-Kyeong Jo:** Conceptualization, Funding acquisition, Writing – review & editing, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

Abreu, R., Essler, L., Loy, A., Quinn, F., Giri, P., 2018. Heparin inhibits intracellular *Mycobacterium tuberculosis* bacterial replication by reducing iron levels in human macrophages. Sci. Rep. 8, 7296.

Cadonic, C., Sabbir, M.G., Albensi, B.C., 2016. Mechanisms of Mitochondrial Dysfunction in Alzheimer's Disease. Mol. Neurobiol. 53, 6078–6090.

Canton, M., Sanchez-Rodriguez, R., Spera, I., Venegas, F.C., Favia, M., Viola, A., Castegna, A., 2021. Reactive oxygen species in macrophages: sources and targets. Front. Immunol. 12, 734229.

Carlos, D., Costa, F.R., Pereira, C.A., Rocha, F.A., Yaochite, J.N., Oliveira, G.G., Carneiro, F.S., Tostes, R.C., Ramos, S.G., Zamboni, D.S., Camara, N.O., Ryffel, B., Silva, J.S., 2017. Mitochondrial DNA activates the NLRP3 inflammasome and predisposes to type 1 diabetes in murine model. Front. Immunol. 8, 164.

Chacon-Salinas, R., Serafin-Lopez, J., Ramos-Payan, R., Mendez-Aragon, P., Hernandez-Pando, R., Van Soolingen, D., Flores-Romo, L., Estrada-Parra, S., Estrada-Garcia, I., 2005. Differential pattern of cytokine expression by macrophages infected in vitro with different *Mycobacterium tuberculosis* genotypes. Clin. Exp. Immunol. 140, 443–449.

Chen, X., Li, C., Cao, X., Jia, X., Chen, X., Wang, Z., Xu, W., Dai, F., Zhang, S., 2022a. Mitochondria-targeted supramolecular coordination container encapsulated with exogenous itaconate for synergistic therapy of joint inflammation. Theranostics 12, 3251–3272.

Chen, Y.M., Liu, P.Y., Tang, K.T., Liu, H.J., Liao, T.L., 2022b. TWEAK-Fn14 axis induces calcium-associated autophagy and cell death to control mycobacterial survival in macrophages. Microbiol. Spectr. 10, e0317222.

Cortassa, S., Aon, M.A., Sollott, S.J., 2019. Control and regulation of substrate selection in cytoplasmic and mitochondrial catabolic networks. A systems biology analysis. Front. Physiol. 10, 201.

Dahl, V.N., Molhave, M., Floe, A., van Ingen, J., Schon, T., Lillebaek, T., Andersen, A.B., Wejse, C., 2022. Global trends of pulmonary infections with nontuberculous mycobacteria: a systematic review. Int. J. Infect. Dis. 125, 120–131.

De Voss, J.J., Rutter, K., Schroeder, B.G., Barry 3rd, C.E., 1999. Iron acquisition and metabolism by mycobacteria. J. Bacteriol. 181, 4443–4451.

Dubey, R.K., Dhamija, E., Kumar Mishra, A., Soam, D., Mohanrao Yabaji, S., Srivastava, K., Srivastava, K.K., 2021. Mycobacterial origin protein Rv0674 localizes into mitochondria, interacts with D-loop and regulates OXPHOS for intracellular persistence of *Mycobacterium tuberculosis*. Mitochondrion 57, 241–256.

Guo, Q., Bi, J., Wang, H., Zhang, X., 2021. *Mycobacterium tuberculosis* ESX-1-secreted substrate protein EspC promotes mycobacterial survival through endoplasmic reticulum stress-mediated apoptosis. Emerg. Microbes Infect. 10, 19–36.

Huang, M.L., Chiang, S., Kalinowski, D.S., Bae, D.H., Sahni, S., Richardson, D.R., 2019. The role of the antioxidant response in mitochondrial dysfunction in degenerative diseases: cross-talk between antioxidant defense, autophagy, and apoptosis. Oxid. Med. Cell. Longev. 2019, 6392763.

Iwasaki, Y., Takeshima, Y., Fujio, K., 2020. Basic mechanism of immune system activation by mitochondria. Immunol. Med. 43, 142–147.

Jo, E.K., Yang, C.S., Choi, C.H., Harding, C.V., 2007. Intracellular signalling cascades regulating innate immune responses to Mycobacteria: branching out from Toll-like receptors. Cell Microbiol. 9, 1087–1098.

Joseph, S., Yuen, A., Singh, V., Hmama, Z., 2017. *Mycobacterium tuberculosis* Cpn60.2 (GroEL2) blocks macrophage apoptosis via interaction with mitochondrial mortalin. Biol. Open 6, 481–488.

Kim, T.S., Jin, Y.B., Kim, Y.S., Kim, S., Kim, J.K., Lee, H.M., Suh, H.W., Choe, J.H., Kim, Y.J., Koo, B.S., Kim, H.N., Jung, M., Lee, S.H., Kim, D.K., Chung, C., Son, J.W., Min, J.J., Kim, J.M., Deng, C.X., Kim, H.S., Lee, S.R., Jo, E.K., 2019. SIRT3 promotes antimycobacterial defenses by coordinating mitochondrial and autophagic functions. Autophagy 15, 1356–1375.

Kim, Y.J., Lee, S.H., Jeon, S.M., Silwal, P., Seo, J.Y., Hanh, B.T.B., Park, J.W., Whang, J., Lee, M.J., Heo, J.Y., Kim, S.H., Kim, J.M., Song, G.Y., Jang, J., Jo, E.K., 2020. Sirtuin 3 is essential for host defense against *Mycobacterium abscessus* infection through regulation of mitochondrial homeostasis. Virulence 11, 1225–1239.

Kim, J.K., Park, E.J., Jo, E.K., 2022. Itaconate, arginine, and gamma-aminobutyric acid: a host metabolite triad protective against mycobacterial infection. Front. Immunol. 13, 832015.

Kim, Y.J., Park, E.J., Lee, S.H., Silwal, P., Kim, J.K., Yang, J.S., Whang, J., Jang, J., Kim, J.M., Jo, E.K., 2023. Dimethyl itaconate is effective in host-directed antimicrobial responses against mycobacterial infections through multifaceted innate immune pathways. Cell Biosci. 13, 49.

Kotey, S.K., Tan, X., Fleming, O., Kasiraju, R.R., Dagnell, A.L., Van Pelt, K.N., Rogers, J., Hartson, S.D., Thadathil, N., Selvarani, R., Ranjit, R., Logan, S., Deepa, S.S., Richardson, A., Cheng, Y., 2023. Intracellular iron accumulation facilitates mycobacterial infection in old mouse macrophages. Geroscience 46, 2739–2754.

Lambert, A.J., Brand, M.D., 2004. Inhibitors of the quinone-binding site allow rapid superoxide production from mitochondrial NADH:ubiquinone oxidoreductase (complex I). J. Biol. Chem. 279, 39414–39420.

Lee, J., Choi, J.A., Cho, S.N., Son, S.H., Song, C.H., 2019. Mitofusin 2-Deficiency Suppresses *Mycobacterium tuberculosis* Survival in Macrophages. Cells 8.

Lee, J.W., Kim, H.W., Yu, A.R., Yoon, H.S., Kang, M., Park, H.W., Lee, S.K., Whang, J., Kim, J.S., 2023b. Differential Immune Responses and Underlying Mechanisms of Metabolic Reprogramming in Smooth and Rough Variants of *Mycobacterium peregrinum* Infections. Pathogens 12, 1446.

Lee, J., Lee, S.A., Son, S.H., Choi, J.A., Nguyen, T.D., Kim, J., Son, D., Song, C.H., 2023a. Impaired mitophagy induces antimicrobial responses in macrophages infected with *Mycobacterium tuberculosis*. Cell Biosci. 13, 158.

Li, W., Zeng, H., Xu, M., Huang, C., Tao, L., Li, J., Zhang, T., Chen, H., Xia, J., Li, C., Li, X., 2021. Oleanolic acid improves obesity-related inflammation and insulin resistance by regulating macrophages activation. Front. Pharmacol. 12, 697483.

Liao, Y., Hussain, T., Liu, C., Cui, Y., Wang, J., Yao, J., Chen, H., Song, Y., Sabir, N., Hussain, M., Zhao, D., Zhou, X., 2019. Endoplasmic reticulum stress induces macrophages to produce IL-1beta during *Mycobacterium bovis* infection via a positive feedback loop between mitochondrial damage and inflammasome activation. Front. Immunol. 10, 268.

Lienard, J., Nobs, E., Lovins, V., Movert, E., Valfridsson, C., Carlsson, F., 2020. The *Mycobacterium marinum* ESX-1 system mediates phagosomal permeabilization and type I interferon production via separable mechanisms. Proc. Natl. Acad. Sci. U.S.A. 117, 1160–1166.

Liu, R., Muliadi, V., Mou, W., Li, H., Yuan, J., Holmberg, J., Chambers, B.J., Ullah, N., Wurth, J., Alzrigat, M., Schlisio, S., Carow, B., Larsson, L.G., Rottenberg, M.E., 2022. HIF-1 stabilization in T cells hampers the control of *Mycobacterium tuberculosis* infection. Nat. Commun. 13, 5093.

Liu, Y., Xu, R., Gu, H., Zhang, E., Qu, J., Cao, W., Huang, X., Yan, H., He, J., Cai, Z., 2021. Metabolic reprogramming in macrophage responses. Biomark Res. 9, 1.

Lloberas, J., Munoz, J.P., Hernandez-Alvarez, M.I., Cardona, P.J., Zorzano, A., Celada, A., 2020. Macrophage mitochondrial MFN2 (mitofusin 2) links immune stress and immune response through reactive oxygen species (ROS) production. Autophagy 16, 2307–2309.

Lundahl, M.L.E., Mitermite, M., Ryan, D.G., Case, S., Williams, N.C., Yang, M., Lynch, R. I., Lagan, E., Lebre, F.M., Gorman, A.L., Stojkovic, B., Bracken, A.P., Frezza, C.,

Sheedy, F.J., Scanlan, E.M., O'Neill, L.A.J., Gordon, S.V., Lavelle, E.C., 2022. Macrophage innate training induced by IL-4 and IL-13 activation enhances OXPHOS driven anti-mycobacterial responses. Elife 11.
Madigan, C.A., Cambier, C.J., Kelly-Scumpia, K.M., Scumpia, P.O., Cheng, T.Y., Zailaa, J., Bloom, B.R., Moody, D.B., Smale, S.T., Sagasti, A., Modlin, R.L., Ramakrishnan, L., 2017. A Macrophage Response to *Mycobacterium leprae* Phenolic Glycolipid Initiates Nerve Damage in Leprosy. Cell 170 (973–985), e910.
Margenat, M., Betancour, G., Irving, V., Costabile, A., Garcia-Cedres, T., Portela, M.M., Carrion, F., Herrera, F.E., Villarino, A., 2023. Characteristics of *Mycobacterium tuberculosis* PtpA interaction and activity on the alpha subunit of human mitochondrial trifunctional protein, a key enzyme of lipid metabolism. Front. Cell. Infect. Microbiol. 13, 1095060.
Marin Franco, J.L., Genoula, M., Corral, D., Duette, G., Ferreyra, M., Maio, M., Dolotowicz, M.B., Aparicio-Trejo, O.E., Patino-Martinez, E., Charton, A., Metais, A., Fuentes, F., Soldan, V., Morana, E.J., Palmero, D., Ostrowski, M., Schierloh, P., Sanchez-Torres, C., Hernandez-Pando, R., Pedraza-Chaverri, J., Rombouts, Y., Hudrisier, D., Layre, E., Verollet, C., Maridonneau-Parini, I., Neyrolles, O., Sasiain, M.D.C., Lugo-Villarino, G., Balboa, L., 2020. Host-Derived Lipids from Tuberculous Pleurisy Impair Macrophage Microbicidal-Associated Metabolic Activity. Cell Rep. 33, 108547.
Martin, M., deVisch, A., Boudehen, Y.M., Barthe, P., Gutierrez, C., Turapov, O., Aydogan, T., Heriaud, L., Gracy, J., Neyrolles, O., Mukamolova, G.V., Letourneur, F., Cohen-Gonsaud, M., 2023. A *Mycobacterium tuberculosis* Effector Targets Mitochondrion, Controls Energy Metabolism, and Limits Cytochrome c Exit. Microbiol. Spectr. 11, e0106623.
Matsumura, K., Takaki, S., Kirikae, T., 2023. Mycobacterial protein PE_PGRS30 induces macrophage apoptosis through prohibitin 2 mitochondrial function interference. Front. Microbiol. 14, 1080369.
Medha, P., Bhatt, P., Sharma, S., Sharma, M., 2023. Role of C-terminal domain of *Mycobacterium tuberculosis* PE6 (Rv0335c) protein in host mitochondrial stress and macrophage apoptosis. Apoptosis 28, 136–165.
Mills, E.L., Kelly, B., Logan, A., Costa, A.S.H., Varma, M., Bryant, C.E., Tourlomousis, P., Dabritz, J.H.M., Gottlieb, E., Latorre, I., Corr, S.C., McManus, G., Ryan, D., Jacobs, H.T., Szibor, M., Xavier, R.J., Braun, T., Frezza, C., Murphy, M.P., O'Neill, L. A., 2016. Succinate dehydrogenase supports metabolic repurposing of mitochondria to drive inflammatory macrophages. Cell 167 (457–470), e413.
Moreira-Teixeira, L., Sousa, J., McNab, F.W., Torrado, E., Cardoso, F., Machado, H., Castro, F., Cardoso, V., Gaifem, J., Wu, X., Appelberg, R., Castro, A.G., O'Garra, A., Saraiva, M., 2016. Type I IFN Inhibits alternative macrophage activation during *Mycobacterium tuberculosis* infection and leads to enhanced protection in the absence of IFN-gamma signaling. J. Immunol. 197, 4714–4726.
Nagy, C., Haschemi, A., 2015. Time and demand are two critical dimensions of immunometabolism: the process of macrophage activation and the pentose phosphate pathway. Front. Immunol. 6, 164.
Nolfi-Donegan, D., Braganza, A., Shiva, S., 2020. Mitochondrial electron transport chain: Oxidative phosphorylation, oxidant production, and methods of measurement. Redox Biol. 37, 101674.
Pajuelo, D., Gonzalez-Juarbe, N., Tak, U., Sun, J., Orihuela, C.J., Niederweis, M., 2018. NAD+ depletion triggers macrophage necroptosis, a cell death pathway exploited by *Mycobacterium tuberculosis*. Cell Rep. 24, 429–440.
Pajuelo, D., Gonzalez-Juarbe, N., Niederweis, M., 2020. NAD hydrolysis by the tuberculosis necrotizing toxin induces lethal oxidative stress in macrophages. Cell Microbiol. 22, e13115.
Pereira, A.C., De Pascale, J., Resende, R., Cardoso, S., Ferreira, I., Neves, B.M., Carrascal, M.A., Zuzarte, M., Madeira, N., Morais, S., Macedo, A., do Carmo, A., Moreira, P.I., Cruz, M.T., Pereira, C.F., 2022. ER-mitochondria communication is involved in NLRP3 inflammasome activation under stress conditions in the innate immune system. Cell. Mol. Life Sci. 79, 213.
Phelan, J.J., Basdeo, S.A., Tazoll, S.C., McGivern, S., Saborido, J.R., Keane, J., 2018. Modulating Iron for Metabolic Support of TB Host Defense. Front. Immunol. 9, 2296.
Remels, A.H., Gosker, H.R., Verhees, K.J., Langen, R.C., Schols, A.M., 2015. TNF-alpha-induced NF-kappaB activation stimulates skeletal muscle glycolytic metabolism through activation of HIF-1alpha. Endocrinology 156, 1770–1781.
Rohde, K.H., Veiga, D.F., Caldwell, S., Balazsi, G., Russell, D.G., 2012. Linking the transcriptional profiles and the physiological states of *Mycobacterium tuberculosis* during an extended intracellular infection. PLoS Pathog. 8, e1002769.
Rost, L.M., Louet, C., Bruheim, P., Flo, T.H., Gidon, A., 2022. Pyruvate Supports RET-Dependent Mitochondrial ROS Production to Control *Mycobacterium avium* Infection in Human Primary Macrophages. Front. Immunol. 13, 891475.
Roy, S., Schmeier, S., Kaczkowski, B., Arner, E., Alam, T., Ozturk, M., Tamgue, O., Parihar, S.P., Kawaji, H., Itoh, M., Lassmann, T., Carninci, P., Hayashizaki, Y., Forrest, A.R.R., Guler, R., Bajic, V.B., Brombacher, F., Suzuki, H., 2018. Transcriptional landscape of *Mycobacterium tuberculosis* infection in macrophages. Sci. Rep. 8, 6758.
Saxena, S., Spaink, H.P., Forn-Cuni, G., 2021. Drug Resistance in Nontuberculous Mycobacteria: Mechanisms and Models. Biology (Basel) 10.
Sena, L.A., Chandel, N.S., 2012. Physiological roles of mitochondrial reactive oxygen species. Mol. Cell 48, 158–167.
Sengupta, N., Padmanaban, S., Dutta, S., 2023. Cryo-EM reveals the membrane-binding phenomenon of EspB, a virulence factor of the mycobacterial type VII secretion system. J. Biol. Chem. 299, 104589.
Shadel, G.S., Horvath, T.L., 2015. Mitochondrial ROS signaling in organismal homeostasis. Cell 163, 560–569.
Shariq, M., Quadir, N., Sharma, N., Singh, J., Sheikh, J.A., Khubaib, M., Hasnain, S.E., Ehtesham, N.Z., 2021. *Mycobacterium tuberculosis* RipA Dampens TLR4-Mediated Host Protective Response Using a Multi-Pronged Approach Involving Autophagy, Apoptosis, Metabolic Repurposing, and Immune Modulation. Front. Immunol. 12, 636644.
Shi, L., Salamon, H., Eugenin, E.A., Pine, R., Cooper, A., Gennaro, M.L., 2015. Infection with *Mycobacterium tuberculosis* induces the Warburg effect in mouse lungs. Sci. Rep. 5, 18176.
Silwal, P., Kim, J.K., Kim, Y.J., Jo, E.K., 2020. Mitochondrial Reactive Oxygen Species: Double-Edged Weapon in Host Defense and Pathological Inflammation During Infection. Front. Immunol. 11, 1649.
Silwal, P., Kim, J.K., Jeon, S.M., Lee, J.Y., Kim, Y.J., Kim, Y.S., Seo, Y., Kim, J., Kim, S.Y., Lee, M.J., Heo, J.Y., Jung, M.J., Kim, H.S., Hyun, D.W., Han, J.E., Whang, J., Huh, Y. H., Lee, S.H., Heo, W.D., Kim, J.M., Bae, J.W., Jo, E.K., 2021. Mitofusin-2 boosts innate immunity through the maintenance of aerobic glycolysis and activation of xenophagy in mice. Commun. Biol. 4, 548.
Singh, V., Chibale, K., 2021. Strategies to Combat Multi-Drug Resistance in Tuberculosis. Acc. Chem. Res. 54, 2361–2376.
Smulan, L.J., Martinez, N., Kiritsy, M.C., Kativhu, C., Cavallo, K., Sassetti, C.M., Singhal, A., Remold, H.G., Kornfeld, H., 2021. Sirtuin 3 Downregulation in *Mycobacterium tuberculosis*-Infected Macrophages Reprograms Mitochondrial Metabolism and Promotes Cell Death. mBio 12, e03140–20.
Sohn, H., Kim, J.S., Shin, S.J., Kim, K., Won, C.J., Kim, W.S., Min, K.N., Choi, H.G., Lee, J. C., Park, J.K., Kim, H.J., 2011. Targeting of *Mycobacterium tuberculosis* heparin-binding hemagglutinin to mitochondria in macrophages. PLoS Pathog. 7, e1002435.
Tur, J., Pereira-Lopes, S., Vico, T., Marin, E.A., Munoz, J.P., Hernandez-Alvarez, M., Cardona, P.J., Zorzano, A., Lloberas, J., Celada, A., 2020. Mitofusin 2 in Macrophages Links Mitochondrial ROS Production, Cytokine Release, Phagocytosis, Autophagy, and Bactericidal Activity. Cell Rep. 32, 108079.
Weindel, C.G., Martinez, E.L., Zhao, X., Mabry, C.J., Bell, S.L., Vail, K.J., Coleman, A.K., VanPortfliet, J.J., Zhao, B., Wagner, A.R., Azam, S., Scott, H.M., Li, P., West, A.P., Karpac, J., Patrick, K.L., Watson, R.O., 2022. Mitochondrial ROS promotes susceptibility to infection via gasdermin D-mediated necroptosis. Cell 185 (3214–3231), e3223.
Wiens, K.E., Ernst, J.D., 2016. The Mechanism for Type I Interferon Induction by *Mycobacterium tuberculosis* is Bacterial Strain-Dependent. PLoS Pathog. 12, e1005809.
Wu, J., Yan, Z., Schwartz, D.E., Yu, J., Malik, A.B., Hu, G., 2013. Activation of NLRP3 inflammasome in alveolar macrophages contributes to mechanical stretch-induced lung inflammation and injury. J. Immunol. 190, 3590–3599.
Xu, C., Yue, Y., Xiong, S., 2023. *Mycobacterium tuberculosis* Rv0928 protein facilitates macrophage control of mycobacterium infection by promoting mitochondrial intrinsic apoptosis and ROS-mediated inflammation. Front. Microbiol. 14, 1291358.
Yang, Y., Zhou, X., Kouadir, M., Shi, F., Ding, T., Liu, C., Liu, J., Wang, M., Yang, L., Yin, X., Zhao, D., 2013. The AIM2 inflammasome is involved in macrophage activation during infection with virulent *Mycobacterium bovis* strain. J. Infect. Dis. 208, 1849–1858.
Yin, M., O'Neill, L.A.J., 2021. The role of the electron transport chain in immunity. FASEB J. 35, e21974.
Zhao, Y., Wang, Z., Feng, D., Zhao, H., Lin, M., Hu, Y., Zhang, N., Lv, L., Gao, Z., Zhai, X., Tian, X., Yao, J., 2019. p66Shc Contributes to Liver Fibrosis through the Regulation of Mitochondrial Reactive Oxygen Species. Theranostics 9, 1510–1522.