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Not too fat to fight – The emerging role of macrophage fatty acid metabolism in immunity to *Mycobacterium tuberculosis*

Thomas Laval[1,2], Lise Chaumont[1] and Caroline Demangel[1*]

[1] Immunobiology of Infection Unit, Institut Pasteur, INSERM U1221, Paris, France

[2] Université de Paris, Sorbonne Paris Cité, Paris, France

*Corresponding author : Caroline Demangel, Institut Pasteur, 25 Rue du Dr Roux, 75724 Paris Cedex 15, France. Phone: 33 (0)1 40 61 30 66; e-mail: demangel@pasteur.fr

Summary

While the existence of a special relationship between *Mycobacterium tuberculosis* (Mtb) and host lipids has long been known, it remains a challenging enigma. It was clearly established that Mtb requires host fatty acids (FAs) and cholesterol to produce energy, build its distinctive lipid-rich cell wall and produce lipid virulence factors. It was also observed that in infected hosts, Mtb constantly resides in a FA-rich environment that the pathogen contributes to generate by inducing a lipid-laden "foamy" phenotype in host macrophages. These observations, and the proximity between lipid droplets and phagosomes containing bacteria within infected macrophages gave rise to the hypothesis that Mtb reprograms host cell lipid metabolism to ensure a continuous supply of essential nutrients and its long-term persistence *in vivo*. However, recent studies question this principle by indicating that in Mtb-infected macrophages, lipid droplet formation prevents bacterial acquisition of host FAs while supporting the production of FA-derived protective lipid mediators. Further, *in vivo* investigations reveal discrete macrophage phenotypes linking the FA metabolisms of host cell and intracellular pathogen. Notably, FA storage within lipid droplets characterizes both macrophages controlling Mtb infection and dormant intracellular Mtb. In this review, we integrate findings from immunological and microbiological studies illustrating the new concept that cytoplasmic accumulation of FAs is a metabolic adaptation of macrophages to Mtb infection, which potentiates their antimycobacterial responses and forces the intracellular pathogen to shift into fat-saving, survival mode.

Introduction

Mycobacterium tuberculosis (Mtb), the causative agent of tuberculosis (TB), has evolved sophisticated strategies to survive intracellularly in lung macrophages and extracellularly within granulomas. High lipid content, including fatty acids (FAs) and cholesterol, is a common denominator of the microenvironments of these two infection sites. The following sections describe how Mtb contributes to their generation and how, in return, host lipids impact on Mtb metabolism and physiology. We then confront these data, mostly generated *in vitro* using cellular models of infection, with the *in vivo* reality of infected animal models. Finally, we highlight current research gaps and the key questions to address in order to progress towards novel anti-tuberculosis (TB) therapies targeting host-lipid metabolism.

I - *Mycobacterium tuberculosis* is constantly exposed to FAs in infected hosts

When aerosols of Mtb penetrate the lungs of a new host, bacilli are phagocytosed by professional alveolar macrophages (AMs) in the lower respiratory tract and start replicating intracellularly. Infected AMs subsequently relocate to the lung interstitium, allowing bacterial dissemination to monocyte-derived macrophages, neutrophils and dendritic cells [1]. Migration of Mtb-infected dendritic cells to the draining lymph nodes initiates adaptive immune responses, leading to the recruitment of monocytes and lymphocytes to the primary site of infection [2]. Immune infiltrates aggregate around Mtb-infected macrophages to form granulomas [3], concentric structures that are pathological hallmarks of mycobacterial diseases. Tuberculous granulomas are characterized by the presence of “foamy” macrophages

harboring dormant bacilli (reviewed in [4]). Their foamy appearance is due to cytoplasmic accumulation of lipid droplets (LDs) that are mainly composed of triacylglycerols (TAGs), a storage form of FAs, and cholesteryl esters [5] (Figure 1).

Tuberculous granulomas often display a central area of caseous necrosis - the caseum - where Mtb bacilli were found to persist extracellularly [6,7]. Rupture of necrotic granulomas releases live Mtb bacilli into the airways, enabling bacterial transmission [8]. Since the lipid composition of TB granulomas [5,6] and sputum from TB patients [9,10] resembles that of LDs, it is believed that the caseum derives from the content of LDs released by dead foamy macrophages. Although Mtb resides primarily within foamy macrophages and the caseous centre of necrotic granulomas, bacilli can also persist in other TAG-rich tissues. Indeed, Mtb was detected in the adipose tissue of patients with active and latent TB, and it was shown that Mtb can infect and survive intracellularly in a non-replicative state within adipocytes [11].

Therefore, whether intracellularly in foamy macrophages or extracellularly within granulomas, Mtb is constantly exposed to a lipid-rich environment during its life cycle in humans. As reviewed in the next section, Mtb contributes to generate this environment by fundamentally reshaping the lipid metabolism of host macrophages and promoting the intracellular accumulation of TAGs.

II - Reprogramming of the metabolism of macrophages by *M. tuberculosis*

Recent advances in gene expression and metabolome profiling have begun to reveal a complex, biphasic remodeling of the metabolism of Mtb-infected macrophages, which is intimately coupled to inflammatory and antimicrobial responses.

a) Reprogramming of energy metabolism

Activation of TLR2/4 by Mtb components was shown to trigger in host macrophages a switch towards aerobic glycolysis within the first 24h of infection (Figure 2). This metabolic shift was associated with inhibition of the tricarboxylic acid (TCA) cycle and reduction in oxidative phosphorylation (OXPHOS) activity [12–14]. Reprogramming of glycolysis involved production of the Hypoxia-Inducible transcription Factor HIF-1α and increased host macrophage ability to restrict intracellular growth of Mtb in both cellular and animal models of infection, *via* a mechanism involving IL-1β [15,16]. Besides, TLR4 activation induces the accumulation of the TCA cycle intermediate succinate, which promotes aerobic glycolysis by boosting HIF-1α activity and the associated production of IL-1β [17]. TLR4 activation also induces a break point in the TCA cycle at isocitrate dehydrogenase (IDH), diverting the cis-aconitate substrate of IDH towards production of itaconate by aconitate decarboxylase, also known as immune-responsive-gene 1 (IRG1) [18]. In macrophages, infection with Mtb downregulated IDH production while increasing expression and activity of IRG1, thus promoting the production of itaconate [19]. Yet, itaconate has anti-inflammatory effects in activated macrophages, through inhibition of the production of inflammatory cytokines and reactive oxygen species (ROS) [20,21]. In addition, itaconate was shown to be a potent inhibitor of isocitrate lyases Icl1/2 in Mtb [22]. Together with malate synthase, mycobacterial Icl1/2 form an anaplerotic pathway called the glyoxylate shunt, which converts the TCA cycle intermediate isocitrate into malate and succinate. Products of the glyoxylate shunt fuel gluconeogenesis in Mtb when FAs are the only available carbon sources, and this metabolic pathway was found critical for bacterial growth *in vivo* [23]. Notably, IRG1-deficient macrophages were defective in their ability to control intracellular Mtb growth [19] and IRG1 expression prevented immunopathology in a mouse

model of Mtb infection [24], demonstrating the importance of this pathway in host defense against Mtb. Reprogramming of aerobic glycolysis and TCA cycle are associated with increased levels of NADPH oxidase and inducible nitric oxide synthase (iNOS), promoting the production of ROS including nitric oxide (NO) with antimycobacterial activity [25,26]. Therefore, the early immunometabolic responses of macrophages to Mtb infection promote Mtb killing (Figure 2).

It is important to note that Mtb has evolved several mechanisms to subvert the immunometabolic response of macrophages to infection (Figure 2). Compared to BCG or dead Mtb, live Mtb decelerated metabolic flux through glycolysis and the TCA cycle in host macrophages, while increasing mitochondrial dependency on exogenous FAs [12]. Unlike the avirulent strain of Mtb H37Ra, infection with virulent H37Rv induced expression of the microRNA (miR-21), which targets a glycolytic enzyme [27]. The resulting defects in glycolysis and production of IL-1β increased Mtb's ability to replicate and persist in resting and IFN-γ-activated macrophages [27]. Of note, overexpression of the cell wall lipids phthiocerol dimycocerosates (PDIMs) by certain multi-drug resistant strains of Mtb impaired the glycolytic reprogramming of host macrophages via an IFN-β-dependent mechanism bypassing the IL-1R signaling pathway [28].

b) <u>Rewiring of lipid metabolism for intracellular accumulation of TAGs</u>

The above-described reprogramming of energy metabolism develops during the first 24h of macrophage infection and resolves thereafter, while a second wave of metabolic changes begins that profoundly modifies the lipid metabolism of macrophages [25]. In addition to its effects on itaconate and succinate (Figure 2), TLR-driven blockade of the TCA cycle favors the accumulation of citrate, whose export from the mitochondria and cytosolic cleavage generates acetyl-CoA that fuels *de novo* synthesis of cholesterol and FAs (Figure 3).

Besides, TLR2 stimulation by mycobacterial cell wall lipoarabinomannan (LAM) was shown to induce macrophage expression of Peroxisome Proliferator-Activated Receptor (PPAR)-γ [29], a transcription factor regulating genes involved in uptake and mobilization of FAs [30,31] (Figure 3). Knocking down PPAR-γ limited the upregulation of low-density lipoprotein receptor CD36 and formation of LDs in infected macrophages, and this coincided with an altered intracellular growth of Mtb [32]. Moreover, PPAR-γ synergized with testicular nuclear receptor 4 (TR4), activated by Mtb-derived ketomycolic acids, to induce LD accumulation in macrophages via an unknown mechanism [33].

Accumulation of TAGs in Mtb-infected macrophages was shown to require autocrine TNF-α receptor signaling, and downstream activation of the caspase cascade and the mammalian target of rapamycin complex 1 (mTORC1) [5]. Although the underlying mechanism was not fully elucidated, TNF-α-mediated accumulation of TAGs was proposed to involve inhibition of autophagy, regulation of transcription factors involved in TAG biosynthesis (e.g. sterol regulatory element-binding proteins, SREBPs) and a mitochondrial dysfunction leading to reduced FA oxidation [5]. Mtb infection also blocked autophagy and associated lipid catabolism in host macrophages by inducing miR-33 via an unknown mechanism [34]. Finally, Mtb decreased LD lipolysis via induction of 3-hydroxybutyrate (3-HB), a metabolite derived from the ketogenesis pathway and generated from acetyl-CoA. Secreted 3-HB activated the G protein-coupled receptor GPR109A, whose signaling resulted in the stabilization of perilipin 1, a coating protein protecting LDs from lipases [35]. The Mtb virulence factor Early-Secreted Antigenic Target (ESAT)-6 was identified as an activator of 3-HB production. ESAT-6 induced glucose uptake as well as the activity of glycolytic enzymes, resulting in accumulation of acetyl-CoA, which was subsequently reoriented towards the generation of 3-HB [35]. Overall, these

studies revealed multiple mechanisms by which Mtb infection promotes LD formation in host macrophages.

Because the presence of foamy macrophages characterizes chronic TB and correlates with pathology, induction of LDs was initially considered a bacterial virulence process ensuring a continuous lipid supply in infected cells [4,35,36]. In support of this hypothesis, intracellular Mtb was shown to import FAs deriving from host TAGs [37]. However, this view was recently challenged by evidence that Mtb loses capacity to acquire host lipids in the presence of IFN-γ induced LDs. In both macrophage and mouse models of Mtb infection, LD formation and maintenance were found to require IFN-γ-driven induction of HIF-1α and its target gene *Hig2*, which inhibits lipolysis [38]. This argues against LDs being a major source of FAs for intracellular Mtb in IFN-γ-activated macrophages, and suggests that LD formation is a host-driven, adaptive immune process of defense. Besides, LDs were found to support the generation of proinflammatory immune responses in mycobacteria-infected macrophages by representing predominant sites of eicosanoid production [4,38,39]. Indeed, Mtb infection triggers rapid mobilization of long-chain FAs from plasma membranes, particularly the poly-unsaturated arachidonic acid (AA), the precursor of eicosanoids [25]. Cyclooxygenases convert AA into prostaglandins and lipoxygenases generate leukotrienes and lipoxins, with distinct immunoregulatory functions. It was shown that prostaglandin E2 promotes mycobacterial control while on the opposite lipoxin A4 decreases mycobacterial resistance, illustrating the dual role of eicosanoids in host response against Mtb infection [40,41]. Finally, recent data indicate that TLR4 stimulation promotes the assembly of host defense proteins (including IFN-inducible effectors and antimicrobial peptides) into LDs [42]. Further, it uncouples LDs from mitochondria, resulting in decreased OXPHOS and increased contacts between LDs and bacteria [42]. While additional studies will be required to determine if such effects occur in Mtb-

infected macrophages, this suggests that LDs may directly participate in innate immunity against Mtb by directly killing intracellular Mtb while mediating metabolic adaptation to infection.

In addition, there is some evidence suggesting that a reduced FA oxidation would enhance host's defense against Mtb. In the cytosol, free FAs released by internalized lipoproteins or by LD lysis are captured by FA binding proteins and thioesterified by the acyl-CoA synthetase. The resulting FA-CoA are conjugated to carnitine by carnitine palmitoyl transferase I (CPT1) and shuttled across the mitochondrial cell wall by a translocase. Within the mitochondria, the carnitine group is removed by CPT2 and FA-CoA are processed through β-oxidation, which generates acetyl-CoA fueling the TCA cycle and reduces flavin adenine dinucleotide FAD (to FADH2) and nicotinamide adeninedinucleotide NAD+ (to NADH). These reduced products directly feed into the respiratory chain to generate ATP. Chemically inhibiting FA oxidation or knocking out CPT2 both restricted Mtb intra-macrophage growth [43,44]. In Mtb-infected macrophages, FA oxidation blockade was associated with an increase in neutral lipid content, suggesting that decreased Mtb growth is not due to limited FA availability. Instead, it was proposed that blockade of FA oxidation generates mitochondrial ROS leading to phagosomal recruitment of NADPH oxidase, thereby promoting xenophagic elimination of Mtb.

Altogether, data presented in this section call into question the notion that foamy macrophages are permissive for Mtb growth. They introduce the new concept that LD formation in Mtb-infected macrophages may benefit the host by preventing Mtb's access to host FAs while supporting the generation of innate immune responses.

III - Effect of the FA environment on Mtb metabolism and biology

The metabolic changes induced by Mtb infection create a lipid-rich environment for the intracellular pathogen. While the mechanisms by which phagosome-contained Mtb gains access to host cell lipids remain largely unknown; *in vitro* and *ex vivo* studies have provided essential insights into how the lipid environment affects the metabolism and physiology of Mtb (Figure 4).

a) FA import and mobilization

Evidence that Mtb's respiration and growth are stimulated by FAs dates back to the 1950s [45,46]. Since then, several studies have characterized the genetic and enzymatic basis of Mtb's ability to import and metabolize FAs [47]. Mtb's uptake of palmitic acid (PA) and oleic acid (OA) was shown to require a dedicated protein machinery named mammalian cell entry (Mce)1, similar in organization to that importing cholesterol (Mce4) [48,49]. The genome of Mtb harbors four *mce* loci (*mce*1-4), all organized as arrays of two *yrbE* genes (A,B) followed by six *mce* genes (A-F), and a variable number of *mam* genes [50]. YrbE proteins are plasma membrane-embedded permeases interacting with a distantly encoded ATPase MceG [51]. MceA-F are cell wall proteins believed to recognize and shuttle lipid substrates across the mycobacterial outer membrane towards YrbE permeases [52]. Mam proteins are putative accessory proteins involved in the formation and/or stability of their respective Mce complexes [47,48]. Interestingly, Mce1 and Mce4 complexes both require the stabilizing protein LucA and the ATPase MceG, indicating that FA and cholesterol imports are coordinated [47,48,53].

Several transcriptome studies reported an increased expression of the bacterial genes involved in FA and cholesterol import during infection of macrophages and mice [54,55], which

collectively suggest that Mtb reprograms its own lipid metabolism during infection to hijack host lipids. In addition to being imported from the environment, FAs can be mobilized by lipolysis of host membrane phospholipids, endogenous or exogenous TAGs reservoirs. Mtb was shown to use host TAGs to synthesize its own TAGs [37]. This process involves LipY, a lipase produced by Mtb upon macrophage infection as both cytoplasmic and secreted forms that hydrolyze bacteria- and host-derived TAGs, respectively [56–58].

Remarkably, Mtb is able to simultaneously co-catabolize different carbon sources including carbohydrates, FAs and cholesterol [59,60]. This metabolic flexibility contrasts with the carbon catabolite repression that enforces a hierarchical use of carbon sources in most bacteria. Metabolic versatility was proposed to facilitate Mtb's adaptation to changing environments, a notion supported by recent metabolomic studies showing the simultaneous utilization of multiple carbon sources by Mtb within macrophages [61]. It should nevertheless be noted that Mtb's import of cholesterol is required for optimal growth and persistence *in vivo* [49].

Notably, cholesterol catabolism generates the highly toxic propionyl-CoA. Accumulation of propionyl-CoA derivatives in Icl1-deficient mutants (unable to metabolize propionyl-CoA, see §b) intoxicated Mtb and inhibited bacterial growth when Mtb was cultivated in a cholesterol-rich medium [62,63]. However, propionyl-CoA toxicity in *Δicl1* mutants was reduced if the culture medium was supplemented with either short-chain (C2-C8), or long-chain saturated FAs (C18-C24), demonstrating that FA uptake can neutralize the deleterious effects of propionyl-CoA excess. Further, incorporation of ^{14}C-FA in PDIMs was increased in mutants grown in propionate-rich media [62]. Since FAs and propionyl-CoA are precursors for the biosynthesis of PDIMs, it was proposed that utilization of host-derived FAs for the synthesis of methyl-branched lipids such as PDIMs provides a sink for toxic propionyl-CoA [62–

[64]. Reversal of cholesterol-dependent growth inhibition could be achieved by providing Mtb with acetate but not glucose as an alternative carbon source, indicating that cholesterol use imposes metabolic constraints [63].

Altogether, these data indicate that the metabolic pressure exerted on Mtb when metabolizing cholesterol can be compensated via complex lipid biosynthesis. The co-dependence of FA and cholesterol metabolism at all levels (uptake, catabolic and anabolic pathways) is likely to be of paramount importance *in vivo*, due to the TAG- and cholesterol-rich environment of Mtb in infected hosts.

b) <u>FAs as carbon and energy sources</u>

β-oxidation of internalized FAs generates acetyl-CoA, while that of cholesterol produces acetyl-CoA and propionyl-CoA [47]. Acetyl-CoA and propionyl-CoA then feed central metabolic pathways (glyoxylate shunt, methyl citrate cycle (MCC) and methylmalonyl pathway) for energy production or biosynthesis of FAs and complex lipids.

In Mtb, β-oxidation of saturated FAs (SFAs) is ensured by the FadAB enzymatic complex [65], with preliminary conversion of monounsaturated FAs (MUFAs) by enoyl CoA isomerases [66]. Expression of genes involved in the glyoxylate shunt was induced in Mtb grown in a culture medium rich in FAs, in alveolar macrophages and in the mouse model of infection [55,67,68]. As described earlier, this metabolic pathway involves the Icl1/2 enzymes (which cleave isocitrate into succinate and glyoxylate) and GlcB malate synthase, which condenses glyoxylate and acetyl-CoA into malate, fueling other metabolic pathways such as gluconeogenesis. The glyoxylate shunt thus constitutes an alternative to the TCA cycle that ensures the metabolization of acetyl-CoA, while avoiding decarboxylation steps and therefore the loss of

carbon in the form of CO_2. It has been suggested that Mtb preferentially uses this pathway *in vivo* due to carbon source limitation [69].

In Mtb, metabolization of propionyl-CoA from the degradation of odd-chain FAs and cholesterol can occur via the MCC, which generates metabolites fueling the TCA cycle [70,71]. This pathway involves 4 specific enzymes including methylcitrate lyase (Icl1-2). The MCC, and more particularly the Icl1-2 bifunctional enzymes, also appear to play a critical role in Mtb survival *in vivo*. The double mutant *Δicl1Δicl2* was unable to grow in both macrophages and mice [23]. Loss of *in vivo* virulence of *Δicl1* mutants was attributed to the accumulation of cholesterol-derived propionyl-CoA, the excess of which is toxic to Mtb [62].

The methylmalonyl pathway is an alternative to the MCC for metabolization of propionyl-CoA [72]. This anaplerotic pathway ensures generation of methylmalonyl-CoA from propionyl-CoA via the action of the propionyl-CoA carboxylase (Pcc) complex, and methylmalonyl-CoA is subsequently converted into succinyl-CoA in the presence of vitamin B12 [72,73]. Succinyl-CoA can then fuel the TCA cycle and interestingly, this pathway is activated when the MCC is non-functional or inhibited [62,72,73].

Taken together, these studies show that Mtb metabolizes lipids for energy production, while limiting the loss of carbon by decarboxylation (glyoxylate shunt) and moderating the risk of intoxication by propionyl-CoA or its derivatives (MCC). FAs, acetyl-CoA and propionyl-CoA can also serve as substrates for the synthesis of mycobacterial cell wall lipids.

c) <u>FAs as precursors of mycobacterial cell envelope</u>

Situated at the host-pathogen interface, the envelope of Mtb not only plays a major role in bacterial physiology, but also in immunomodulation and tolerance to antibiotics. In

mycobacteria, this envelope is particularly thick and impermeable, with a conventional plasma membrane covered by a complex, lipid-rich cell wall and a capsule mainly composed of polysaccharides and proteins [74]. The cell wall itself is a complex structure composed of superposed layers of peptidoglycan, arabinogalactan and mycolic acids, FAs with exceptionally-long chains whose bilayer organization forms the so-called mycomembrane (Figure 4). This outer membrane also contains non-covalently linked lipoglycans and lipids with pathogenic and immunosuppressive properties, such as PDIMs, phenolic glycolipids and lipoarabinomannan [75,76]. By combining data from *in vitro* and *in vivo* transcriptional and lipidomic studies, Dulberger *et al.* proposed that the mycobacterial wall may be dynamically remodeled during infection, displaying a relatively high content of immunostimulatory lipids at early stages (thus promoting granuloma formation) that decreases thereafter, as the proportion of immunosuppressive lipids such as PDIMs augments [77].

FAs are precursors of various mycobacterial cell wall lipids that can either be *de novo* synthetized by Mtb (endogenous FAs), or imported from the host cell (exogenous FAs) (Figure 4). Similar to eukaryotes, Mtb can synthetize medium- to long-chain saturated FAs from acetyl-CoA via malonyl-CoA generation by acetyl-CoA carboxylase ACC, followed by iterative elongation by the FA synthase-I (FAS-I) enzyme [78]. FAS-I is homologous to the eukaryotic FASN system, and generates 16-22 carbon-long saturated SFAs. C16- and C18-SFAs may then be converted into MUFAs through action of stearoyl-CoA desaturase DesA3 (Rv3229c) coupled to an NADPH oxidoreductase (Rv3230c) [79]. DesA3 is essential for long-term persistence of Mtb *in vivo* [80] and is the target of second-line anti-TB drug isoxyl [81]. Two other desaturases (DesA1 and DesA2) were identified in Mtb that contribute to mycolic acid biosynthesis [50,82]. *De novo* synthesized or exogenous SFAs and MUFAs can be incorporated in plasma membrane phospholipids or cytoplasmic TAGs, the major components of mycobacterial LDs. They can

also serve as precursors for the biosynthesis of cell wall methyl-branched lipids like PDIMs by polyketide synthases (Pks) [83].

Unlike FAS-I, Pks preferentially use propionyl-CoA-derived-methylmalonyl-CoA for FA elongation, thereby introducing methyl branches into FA aliphatic chains [84]. Mtb can elongate further endogenous FAS-I products or exogenous long-chain FAs into very long-chain FAs (22 to 62 carbons) named meromycolic acids via the prokaryote-specific FAS-II enzymatic complex [78]. Pks13-mediated condensation of such meromycolic acids with carboxylated forms of FA-CoA deriving from FAS-I reactions and trehalose yields mycolic acids and trehalose mycolates composing the outer membrane of the cell wall [85,86].

FAs being both precursors of the structured lipids composing the mycobacterial cell wall and important energy-storage molecules, FAS-I and FAS-II play a central role in Mtb physiology and virulence. Genetic manipulation of enzymes in the FAS-II system, or those of the meromycolic acid condensation pathway, impacts mycolic acid layer integrity and bacterial viability [87–89]. FAS-I is essential for mycobacterial survival [90] and is the target of first line anti-TB drug pyrazinamide [91]. The enoyl-acyl carrier protein reductase InhA is an enzyme of the FAS-II system that is targeted by the first-line anti-TB drug isoniazid and its structural analog ethionamide [92]. FasR and MabR are transcriptional regulators of the FAS-I and FAS-II operons that are essential for mycobacterial viability [93,94]. Interestingly, a *fasI* conditional mutant in *M. smegmatis* was defective for biosynthesis of FAs and TAGs, and for bacterial growth in axenic cultures [90]. However, suppressing *fasI* expression did not prevent bacterial production of mycolic acids. In fact, it upregulated the expression of genes involved in the FAS-II pathway. The decreased pool of FAS-I-derived FAs that normally fuels mycolic acid synthesis was compensated by the mobilization of FAs from cytoplasmic TAGs. In addition to revealing

the critical importance of FA biosynthesis for maintenance of cell wall lipid homeostasis, this study highlighted a compensatory crosstalk between the two FAS pathways.

d) FAs, TAG accumulation and quiescence

Intra-phagosomal Mtb must adapt its central metabolism to cope with hypoxia, oxidative and nitrosative stress, as well as acidic pH [95,96]. When mimicked *in vitro*, these conditions dramatically decreased Mtb growth rate, inducing a quiescent state (also referred to as dormant) associated with a switch to anaerobic metabolism [97]. This metabolic shift was driven by the nitric oxide (NO)- and hypoxia-sensitive dormancy survival regulator (DosR) [98,99]. DosR-mediated quiescence supports survival in hypoxic conditions and confers Mtb with an increased tolerance to drugs. Quiescent Mtb can re-initiate a replicative state when environmental conditions improve, and the metabolic reprogramming that is associated with dormancy creates conditions anticipating re-activation. Indeed, hypoxia was shown to induce the accumulation of glycolytic and pentose phosphate pathway intermediates deriving from cell wall trehalose mycolates, which provide building blocks for *de novo* synthesis of peptidoglycan upon re-initiation of replication [100]. More generally, Mtb's entry into dormancy redirects carbon fluxes from energy-generating pathways to anabolic pathways dedicated to storage [71]. Hypoxia, oxidative stress and low iron caused TAG accumulation by Mtb *in vitro*, and Mtb deriving from TB patient sputa displayed a 'fat' phenotype [8,101,102]. Stress-driven TAG accumulation was associated with transcriptional upregulation of TAG synthase Tgs1, and Tgs1 was required for TAG biosynthesis both *in vitro* and in a macrophage infection model [101,103]. A Tgs1-deficient mutant of Mtb was unable to arrest growth in response to stress and remained sensitive to antibiotics during infection, showing that TAG synthesis contributes to antibiotic tolerance *in vivo* [97]. Since acetyl-CoA fuels the FAS-I system, thereby generating FAs

for TAG biosynthesis, it was proposed that stress-induced TAG biosynthesis diverts acetyl-CoA away from the TCA cycle.

In contrast to TAGs, production of most bacterial cell wall lipids is downregulated during dormancy [104,105], suggesting that stress signals reprogram FA metabolism of Mtb towards TAG storage. Reciprocally, a sharp drop in the TAG content of dormant Mtb was observed upon re-aeration. TAG degradation was paralleled by transcriptional upregulation of genes involved in β-oxidation and energy metabolism. It correlated with an increased biosynthesis of most phospholipids and mycolic acids, which are necessary for bacterial replication [104,105]. FA oxidation fuels the glyoxylate shunt, generating precursors for the TCA cycle and gluconeogenesis. Both the glyoxylate and gluconeogenic pathways were required for Mtb persistence *in vivo* [23,60,106,107], highlighting the importance of TAG-derived FAs for maintenance of infection.

Notably, host-derived FAs may directly contribute to Mtb's adaptation to host-associated stresses. When grown on long-chain SFAs and MUFAs as their sole carbon sources, Mtb entered a slowly growing and drug-tolerant physiological state resembling stress-induced quiescence. Interestingly, the dormant signature of FA-exposed Mtb was associated with an increased expression of genes related to reductive stress [68]. It was proposed that FAs force β-oxidation, leading to the accumulation of reducing equivalents and therefore redox imbalance in Mtb. Induction of reductive stress by FAs lowered Mtb's susceptibility to hypoxia, suggesting that FAs reprogram the metabolism of Mtb for adaptation to environmental conditions encountered within the host [108]. Importantly, dormancy also makes Mtb phenotypically resistant to drug treatment. Indeed, most of anti-TB drugs target processes essential for growth, such as DNA replication, translation, cell wall formation [109] that are inactive in dormant Mtb.

These studies illustrate several mechanisms of metabolic adaptation that are used by Mtb to promote long term persistence *in vivo*. Mtb's ability to simultaneously co-catabolize different carbon sources facilitates adaptation to the variable host environment. Biosynthesis of methyl-branched lipids (e.g. PDIMs) limits the reductive stress that is generated by β-oxidation of FAs, and the toxicity of propionyl-CoA that is associated with cholesterol assimilation. Dynamic remodeling of the lipid composition of the mycobacterial cell envelope during the course of infection may allow Mtb to manipulate the human immune system and better tolerate antibiotic treatment. Finally, Mtb ensures survival in hostile, nutrient poor, environments by storing TAGs and entering a state of dormancy.

IV - Metabolic profiles of Mtb and host macrophages *in vivo*

While *in vitro* studies using macrophage models generated useful mechanistic information, they do not reflect the heterogeneity of the macrophage populations in Mtb-infected lungs. Studies using non-human primates and mouse models of Mtb infection indeed identified distinct, permissive and controller macrophage phenotypes corresponding to alveolar (AMs) and interstitial (IMs) macrophages, respectively [43,110]. AM and IM have a different ontogenic origin: while AMs are embryonic-derived cells, IMs derive from blood monocytes recruited upon Mtb infection [111,112]. Strikingly, permissive AMs and controller IMs displayed different metabolic signatures (Figure 5). IMs displayed a marked commitment to aerobic glycolysis associated with pro-inflammatory responses, reflected by elevated expression of IL-1β, TNFα, iNOS and HIF1-α, as well as higher NO and ROS levels. IMs also displayed reduced expression of genes involved in lipid catabolism. In contrast, AMs had a transcriptional profile associated

with OXPHOS and lipid uptake (regulated by the PPAR-γ signaling pathway), TAG degradation, lipolysis and FA oxidation, at the expense of glycolysis and pro-inflammatory responses [43,55].

Induction of a DosR-related stress response in Mtb was recently reported in pro-inflammatory, glycolytically-shifted IMs sorted from infected mouse lungs [55]. This transcriptional profile was associated with slowed replication, resembling that of Mtb subjected to hypoxic stress, NO or low-iron conditions. In comparison, Mtb isolated from anti-inflammatory, FA oxidation/OXPHOS-shifted AMs displayed dampened induction of stress-related genes and a higher expression of genes involved in bacterial division, ribosomal protein and cell wall synthesis, a transcriptional profile consistent with high replication rates. Genes involved in FA uptake, mycolic acid biosynthesis, TCA cycle and FA oxidation were up-regulated in AM-derived bacilli, suggesting that FA catabolism is used to fuel bacterial division. These studies suggested for the first time that macrophage ontology may be a major determinant of the innate immune control of Mtb infection.

V - Conclusions and perspectives for TB treatment

Despite the discovery of effective antibiotic treatments and vaccination with Bacillus Calmette-Guérin (BCG), TB remains the leading cause of death by a single infectious agent and it is estimated that 23% of the world's population has a latent TB infection [113,114]. Moreover, with an estimated 4.1% new cases in 2016, multidrug resistant-tuberculosis (MDR-TB) represents a major obstacle to effective care and prevention world-wide [113]. In this context,

host-directed therapies are emerging as promising anti-TB approaches with potential to improve MDR-TB treatment outcomes.

Recent insights into the metabolic interplay between Mtb and host macrophage have changed our conception of successful innate immune responses, bringing the immunometabolic crosstalk into the forefront. The emerging model divides host-pathogen interactions into permissive or restrictive, depending on the metabolic commitment of infected macrophages to either aerobic glycolysis or FA oxidation. Studies by Huang *et al.* indicated that ontogeny dictates the immunometabolic response of macrophages during the first weeks of infection with Mtb [43]. It will be interesting to determine if cytokines produced by cells involved in adaptive immunity (such as IFN-γ), or other immune-driven factors, can rewire the immunometabolism of permissive macrophages *in vivo* to render them more restrictive.

Strikingly, this functional dichotomy not only links the metabolic profile of macrophages with their inflammatory cytokine and antimicrobial responses, but also with the induction of quiescence and drug tolerance programs in Mtb. With regard to FAs, it is interesting to note that intracellular Mtb and host macrophages reprogram their metabolism in duo. 'Controller' macrophages and intracellular quiescent Mtb both direct FAs towards storage within TAGs, while 'permissive' macrophages and intracellularly replicating Mtb actively degrade FAs via β-oxidation. This suggests an interdependent relationship between the FA metabolisms of Mtb and host macrophages, and potentially common mechanisms of regulation. Recent investigations support the view that in macrophages, rewiring of FA metabolism towards storage in LDs potentiates their ability to restrict the intracellular growth of Mtb in several ways: by limiting bacterial acquisition of host FAs, clustering various antimicrobial factors in LDs, promoting the synthesis of protective eicosanoids and limiting

the flux of FAs through β-oxidation. How precisely does FA metabolism reprogramming in host macrophages induce FA storage within intracellular Mtb remains unclear.

Moreover, little is known about how Mtb gains access to host FAs. Knight *et al.* reported that in resting macrophages, Mtb imports FAs in the absence of LDs [38]. This suggests that Mtb has ability to acquire FAs derived from endocytosed lipoproteins, or from lipids composing the phagosomal membrane. Studies of FA uptake by intracellular Mtb have so far used exogenously added palmitate (a SFA) or oleate (a MUFA), whose anabolic pathways are conserved from bacteria to humans. However, mammals synthesize an additional subset of poly-unsaturated FAs (PUFAs), playing important immunoregulatory functions in activated macrophages through generation of eicosanoids. Whether PUFAs synthesized upon infection with Mtb traffic to phagosomes in infected macrophages and can be metabolized by the intracellular pathogen is unknown. In all, a better understanding of the mechanisms regulating FA fluxes at the host-pathogen interface and an increased appreciation of the importance of FA chemistry in co-metabolism, may help identify novel targets within FA metabolic pathways. It could also lead to the design of innovative anti-TB approaches potentiating immune responses and also limiting the development of antibiotic resistance.

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References

1. Cohen SB, Gern BH, Delahaye JL, et al. Alveolar Macrophages Provide an Early Mycobacterium tuberculosis Niche and Initiate Dissemination. *Cell Host Microbe*. 2018. doi:10.1016/j.chom.2018.08.001
2. Ernst JD. The immunological life cycle of tuberculosis. *Nat Rev Immunol*. 2012;12(8):581-591. doi:10.1038/nri3259
3. Orme IM, Basaraba RJ. The formation of the granuloma in tuberculosis infection. *Semin Immunol*. 2014. doi:10.1016/j.smim.2014.09.009
4. Russell DG, Cardona PJ, Kim MJ, Allain S, Altare F. Foamy macrophages and the progression of the human tuberculosis granuloma. *Nat Immunol*. 2009. doi:10.1038/ni.1781
5. Guerrini V, Prideaux B, Blanc L, et al. Storage lipid studies in tuberculosis reveal that foam cell biogenesis is disease-specific. *PLOS Pathog*. 2018;14(8):e1007223. doi:10.1371/journal.ppat.1007223
6. Kim M-J, Wainwright HC, Locketz M, et al. Caseation of human tuberculosis granulomas correlates with elevated host lipid metabolism. *EMBO Mol Med*. 2010;2(7):258-274. doi:10.1002/emmm.201000079
7. Russell DG, VanderVen BC, Lee W, et al. Mycobacterium tuberculosis wears what it eats. *Cell Host Microbe*. 2010. doi:10.1016/j.chom.2010.06.002
8. Garton NJ, Waddell SJ, Sherratt AL, et al. Cytological and transcript analyses reveal fat and lazy persister-like bacilli in tuberculous sputum. *PLoS Med*. 2008;5(4):e75. doi:10.1371/journal.pmed.0050075
9. Cha D, Cheng D, Liu M, Zeng Z, Hu X, Guan W. Analysis of fatty acids in sputum from

patients with pulmonary tuberculosis using gas chromatography-mass spectrometry preceded by solid-phase microextraction and post-derivatization on the fiber. *J Chromatogr A*. 2009;1216(9):1450-1457. doi:10.1016/j.chroma.2008.12.039

10. Mourão MPB, Denekamp I, Kuijper S, Kolk AHJ, Janssen H-G. Hyphenated and comprehensive liquid chromatography × gas chromatography-mass spectrometry for the identification of Mycobacterium tuberculosis. *J Chromatogr A*. 2016;1439:152-160. doi:10.1016/j.chroma.2015.10.054
11. Neyrolles O, Hernández-Pando R, Pietri-Rouxel F, et al. Is adipose tissue a place for Mycobacterium tuberculosis persistence? *PLoS One*. 2006. doi:10.1371/journal.pone.0000043
12. Cumming BM, Addicott KW, Adamson JH, Steyn AJC. Mycobacterium tuberculosis induces decelerated bioenergetic metabolism in human macrophages. *Elife*. 2018. doi:10.7554/eLife.39169
13. Shi L, Salamon H, Eugenin EA, Pine R, Cooper A, Gennaro ML. Infection with Mycobacterium tuberculosis induces the Warburg effect in mouse lungs. *Sci Rep*. 2015;5:18176. doi:10.1038/srep18176
14. Lachmandas E, Beigier-Bompadre M, Cheng S-C, et al. Rewiring cellular metabolism via the AKT/mTOR pathway contributes to host defence against Mycobacterium tuberculosis in human and murine cells. *Eur J Immunol*. 2016;46(11):2574-2586. doi:10.1002/eji.201546259
15. Braverman J, Sogi KM, Benjamin D, Nomura DK, Stanley SA. HIF-1α Is an Essential Mediator of IFN-γ-Dependent Immunity to Mycobacterium tuberculosis. *J Immunol (Baltimore, Md 1950)*. 2016;197(4):1287-1297. doi:10.4049/jimmunol.1600266
16. Gleeson LE, Sheedy FJ, Palsson-McDermott EM, et al. Cutting Edge: Mycobacterium

tuberculosis Induces Aerobic Glycolysis in Human Alveolar Macrophages That Is Required for Control of Intracellular Bacillary Replication. *J Immunol (Baltimore, Md 1950)*. 2016;196(6):2444-2449. doi:10.4049/jimmunol.1501612

17. Tannahill GM, Curtis AM, Adamik J, et al. Succinate is an inflammatory signal that induces IL-1β through HIF-1α. *Nature*. 2013;496(7444):238-242. doi:10.1038/nature11986

18. O'Neill LAJ, Artyomov MN. Itaconate: the poster child of metabolic reprogramming in macrophage function. *Nat Rev Immunol*. 2019. doi:10.1038/s41577-019-0128-5

19. Hoffmann E, Machelart A, Belhaouane I, et al. IRG1 controls immunometabolic host response and restricts intracellular Mycobacterium tuberculosis infection. *bioRxiv*. May 2019:761551. doi:10.1101/761551

20. Mills EL, Ryan DG, Prag HA, et al. Itaconate is an anti-inflammatory metabolite that activates Nrf2 via alkylation of KEAP1. *Nature*. 2018;556(7699):113-117. doi:10.1038/nature25986

21. Lampropoulou V, Sergushichev A, Bambouskova M, et al. Itaconate Links Inhibition of Succinate Dehydrogenase with Macrophage Metabolic Remodeling and Regulation of Inflammation. *Cell Metab*. 2016;24(1):158-166. doi:10.1016/j.cmet.2016.06.004

22. Michelucci A, Cordes T, Ghelfi J, et al. Immune-responsive gene 1 protein links metabolism to immunity by catalyzing itaconic acid production. *Proc Natl Acad Sci U S A*. 2013;110(19):7820-7825. doi:10.1073/pnas.1218599110

23. Muñoz-Elías EJ, McKinney JD. Mycobacterium tuberculosis isocitrate lyases 1 and 2 are jointly required for in vivo growth and virulence. *Nat Med*. 2005;11(6):638-644. doi:10.1038/nm1252

24. Nair S, Huynh JP, Lampropoulou V, et al. Irg1 expression in myeloid cells prevents

immunopathology during M. tuberculosis infection. *J Exp Med*. 2018;215(4):1035-1045. doi:10.1084/jem.20180118

25. Shi L, Jiang Q, Bushkin Y, Subbian S, Tyagi S. Biphasic Dynamics of Macrophage Immunometabolism during Mycobacterium tuberculosis Infection. *MBio*. 2019;10(2). doi:10.1128/mBio.02550-18

26. Mills EL, Kelly B, Logan A, et al. Succinate Dehydrogenase Supports Metabolic Repurposing of Mitochondria to Drive Inflammatory Macrophages. *Cell*. 2016. doi:10.1016/j.cell.2016.08.064

27. Hackett EE, Charles-Messance H, O'Leary SM, et al. Mycobacterium tuberculosis Limits Host Glycolysis and IL-1β by Restriction of PFK-M via MicroRNA-21. *Cell Rep*. 2020;30(1):124-136.e4. doi:10.1016/j.celrep.2019.12.015

28. Howard NC, Marin ND, Ahmed M, et al. Mycobacterium tuberculosis carrying a rifampicin drug resistance mutation reprograms macrophage metabolism through cell wall lipid changes. *Nat Microbiol*. 2018;3(10):1099-1108. doi:10.1038/s41564-018-0245-0

29. Almeida PE, Silva AR, Maya-Monteiro CM, et al. Mycobacterium bovis bacillus Calmette-Guérin infection induces TLR2-dependent peroxisome proliferator-activated receptor gamma expression and activation: functions in inflammation, lipid metabolism, and pathogenesis. *J Immunol (Baltimore, Md 1950)*. 2009;183(2):1337-1345. doi:10.4049/jimmunol.0900365

30. Chawla A, Barak Y, Nagy L, Liao D, Tontonoz P, Evans RM. PPAR-gamma dependent and independent effects on macrophage-gene expression in lipid metabolism and inflammation. *Nat Med*. 2001;7(1):48-52. doi:10.1038/83336

31. Moore KJ, Rosen ED, Fitzgerald ML, et al. The role of PPAR-gamma in macrophage

differentiation and cholesterol uptake. *Nat Med*. 2001;7(1):41-47. doi:10.1038/83328

32. Mahajan S, Dkhar HK, Chandra V, et al. Mycobacterium tuberculosis modulates macrophage lipid-sensing nuclear receptors PPARγ and TR4 for survival. *J Immunol (Baltimore, Md 1950)*. 2012;188(11):5593-5603. doi:10.4049/jimmunol.1103038

33. Dkhar HK, Nanduri R, Mahajan S, et al. Mycobacterium tuberculosis keto-mycolic acid and macrophage nuclear receptor TR4 modulate foamy biogenesis in granulomas: a case of a heterologous and noncanonical ligand-receptor pair. *J Immunol (Baltimore, Md 1950)*. 2014;193(1):295-305. doi:10.4049/jimmunol.1400092

34. Ouimet M, Koster S, Sakowski E, et al. Mycobacterium tuberculosis induces the miR-33 locus to reprogram autophagy and host lipid metabolism. *Nat Immunol*. 2016;17(6):677-686. doi:10.1038/ni.3434

35. Singh V, Jamwal S, Jain R, Verma P, Gokhale R, Rao KVS. Mycobacterium tuberculosis-driven targeted recalibration of macrophage lipid homeostasis promotes the foamy phenotype. *Cell Host Microbe*. 2012;12(5):669-681. doi:10.1016/j.chom.2012.09.012

36. Peyron P, Vaubourgeix J, Poquet Y, et al. Foamy macrophages from tuberculous patients' granulomas constitute a nutrient-rich reservoir for M. tuberculosis persistence. *PLoS Pathog*. 2008. doi:10.1371/journal.ppat.1000204

37. Daniel J, Maamar H, Deb C, Sirakova TD, Kolattukudy PE. Mycobacterium tuberculosis uses host triacylglycerol to accumulate lipid droplets and acquires a dormancy-like phenotype in lipid-loaded macrophages. *PLoS Pathog*. 2011. doi:10.1371/journal.ppat.1002093

38. Knight M, Braverman J, Asfaha K, Gronert K, Stanley S. Lipid droplet formation in Mycobacterium tuberculosis infected macrophages requires IFN-γ/HIF-1α signaling and supports host defense. *PLoS Pathog*. 2018;14(1):e1006874.

doi:10.1371/journal.ppat.1006874

39. D'Avila H, Melo RCN, Parreira GG, Werneck-Barroso E, Castro-Faria-Neto HC, Bozza PT. Mycobacterium bovis bacillus Calmette-Guérin induces TLR2-mediated formation of lipid bodies: intracellular domains for eicosanoid synthesis in vivo. *J Immunol (Baltimore, Md 1950)*. 2006;176(5):3087-3097. doi:10.4049/jimmunol.176.5.3087

40. Dietzold J, Gopalakrishnan A, Salgame P. Duality of lipid mediators in host response against Mycobacterium tuberculosis: Good cop, bad cop. *F1000Prime Rep*. 2015. doi:10.12703/P7-29

41. Mayer-Barber KD, Sher A. Cytokine and lipid mediator networks in tuberculosis. *Immunol Rev*. 2015. doi:10.1111/imr.12249

42. Bosch M, Sánchez-Álvarez M, Fajardo A, et al. Mammalian lipid droplets are innate immune hubs integrating cell metabolism and host defense. *Science*. 2020. doi:10.1126/science.aay8085

43. Huang L, Nazarova E V., Tan S, Liu Y, Russell DG. Growth of Mycobacterium tuberculosis in vivo segregates with host macrophage metabolism and ontogeny. *J Exp Med*. 2018. doi:10.1084/jem.20172020

44. Chandra P, He L, Zimmerman M, et al. Inhibition of Fatty Acid Oxidation Promotes Macrophage Control of Mycobacterium tuberculosis. *MBio*. 2020. doi:10.1128/mBio.01139-20

45. Dubos RJ. The effect of organic acids on mammalian tubercle bacilli. *J Exp Med*. 1950;92(4):319-332. doi:10.1084/jem.92.4.319

46. Davis BD, Dubos RJ. THE BINDING OF FATTY ACIDS BY SERUM ALBUMIN, A PROTECTIVE GROWTH FACTOR IN BACTERIOLOGICAL MEDIA. *J Exp Med*. 1947.

47. Wilburn KM, Fieweger RA, VanderVen BC. Cholesterol and fatty acids grease the

wheels of Mycobacterium tuberculosis pathogenesis. *Pathog Dis*. 2018. doi:10.1093/femspd/fty021

48. Nazarova E V., Montague CR, La T, et al. Rv3723/LucA coordinates fatty acid and cholesterol uptake in Mycobacterium tuberculosis. *Elife*. 2017. doi:10.7554/eLife.26969

49. Pandey AK, Sassetti CM. Mycobacterial persistence requires the utilization of host cholesterol. *Proc Natl Acad Sci U S A*. 2008. doi:10.1073/pnas.0711159105

50. Cole ST, Brosch R, Parkhill J, et al. Deciphering the biology of Mycobacterium tuberculosis from the complete genome sequence [see comments] [published erratum appears in Nature 1998 Nov 12;396(6707):190]. *Nature*. 1998.

51. Casali N, Riley LW. A phylogenomic analysis of the Actinomycetales mce operons. *BMC Genomics*. 2007. doi:10.1186/1471-2164-8-60

52. Ekiert DC, Bhabha G, Isom GL, et al. Architectures of Lipid Transport Systems for the Bacterial Outer Membrane. *Cell*. 2017. doi:10.1016/j.cell.2017.03.019

53. Nazarova E V, Russell D, VanderVen BC, Huang L, Montague CR, La T. The genetic requirements of fatty acid import by Mycobacterium tuberculosis within macrophages. *Elife*. 2019. doi:10.7554/elife.43621

54. Rohde KH, Veiga DFT, Caldwell S, Balázsi G, Russell DG. Linking the transcriptional profiles and the physiological states of Mycobacterium tuberculosis during an extended intracellular infection. *PLoS Pathog*. 2012;8(6):e1002769. doi:10.1371/journal.ppat.1002769

55. Pisu D, Huang L, Grenier JK, Russell DG. Dual RNA-Seq of Mtb-Infected Macrophages In Vivo Reveals Ontologically Distinct Host-Pathogen Interactions. *Cell Rep*. 2020;30(2):335-350.e4. doi:10.1016/j.celrep.2019.12.033

56. Deb C, Daniel J, Sirakova TD, Abomoelak B, Dubey VS, Kolattukudy PE. A novel lipase belonging to the hormone-sensitive lipase family induced under starvation to utilize stored triacylglycerol in Mycobacterium tuberculosis. *J Biol Chem*. 2006;281(7):3866-3875. doi:10.1074/jbc.M505556200

57. Santucci P, Smichi N, Diomandé S, et al. Dissecting the membrane lipid binding properties and lipase activity of Mycobacterium tuberculosis LipY domains. *FEBS J*. 2019;286(16):3164-3181. doi:10.1111/febs.14864

58. Daleke MH, Cascioferro A, de Punder K, et al. Conserved Pro-Glu (PE) and Pro-Pro-Glu (PPE) protein domains target LipY lipases of pathogenic mycobacteria to the cell surface via the ESX-5 pathway. *J Biol Chem*. 2011;286(21):19024-19034. doi:10.1074/jbc.M110.204966

59. de Carvalho LPS, Fischer SM, Marrero J, Nathan C, Ehrt S, Rhee KY. Metabolomics of Mycobacterium tuberculosis reveals compartmentalized co-catabolism of carbon substrates. *Chem Biol*. 2010;17(10):1122-1131. doi:10.1016/j.chembiol.2010.08.009

60. Marrero J, Trujillo C, Rhee KY, Ehrt S. Glucose phosphorylation is required for Mycobacterium tuberculosis persistence in mice. *PLoS Pathog*. 2013;9(1):e1003116. doi:10.1371/journal.ppat.1003116

61. Zimmermann M, Kogadeeva M, Gengenbacher M, et al. Integration of Metabolomics and Transcriptomics Reveals a Complex Diet of Mycobacterium tuberculosis during Early Macrophage Infection. *mSystems*. 2017;2(4). doi:10.1128/mSystems.00057-17

62. Lee W, VanderVen BC, Fahey RJ, Russell DG. Intracellular Mycobacterium tuberculosis exploits host-derived fatty acids to limit metabolic stress. *J Biol Chem*. 2013. doi:10.1074/jbc.M112.445056

63. VanderVen BC, Fahey RJ, Lee W, et al. Novel inhibitors of cholesterol degradation in

Mycobacterium tuberculosis reveal how the bacterium's metabolism is constrained by the intracellular environment. *PLoS Pathog*. 2015;11(2):e1004679. doi:10.1371/journal.ppat.1004679

64. Fieweger RA, Wilburn KM, Vanderven BC. Comparing the metabolic capabilities of bacteria in the mycobacterium tuberculosis complex. *Microorganisms*. 2019. doi:10.3390/microorganisms7060177

65. Venkatesan R, Wierenga RK. Structure of mycobacterial β-oxidation trifunctional enzyme reveals its altered assembly and putative substrate channeling pathway. *ACS Chem Biol*. 2013;8(5):1063-1073. doi:10.1021/cb400007k

66. Srivastava S, Chaudhary S, Thukral L, et al. Unsaturated Lipid Assimilation by Mycobacteria Requires Auxiliary cis-trans Enoyl CoA Isomerase. *Chem Biol*. 2015;22(12):1577-1587. doi:10.1016/j.chembiol.2015.10.009

67. Schnappinger D, Ehrt S, Voskuil MI, et al. Transcriptional Adaptation of Mycobacterium tuberculosis within Macrophages: Insights into the Phagosomal Environment. *J Exp Med*. 2003;198(5):693-704. doi:10.1084/jem.20030846

68. Rodríguez JG, Hernández AC, Helguera-Repetto C, et al. Global adaptation to a lipid environment triggers the dormancy-related phenotype of Mycobacterium tuberculosis. *MBio*. 2014;5(3):e01125-01114. doi:10.1128/mBio.01125-14

69. Ehrt S, Schnappinger D, Rhee KY. Metabolic principles of persistence and pathogenicity in Mycobacterium tuberculosis. *Nat Rev Microbiol*. 2018;16(8):496-507. doi:10.1038/s41579-018-0013-4

70. Muñoz-Elías EJ, Upton AM, Cherian J, McKinney JD. Role of the methylcitrate cycle in Mycobacterium tuberculosis metabolism, intracellular growth, and virulence. *Mol Microbiol*. 2006. doi:10.1111/j.1365-2958.2006.05155.x

71. Shi L, Sohaskey CD, Pheiffer C, et al. Carbon flux rerouting during Mycobacterium tuberculosis growth arrest. *Mol Microbiol*. 2010;78(5):1199-1215. doi:10.1111/j.1365-2958.2010.07399.x

72. Savvi S, Warner DF, Kana BD, McKinney JD, Mizrahi V, Dawes SS. Functional characterization of a vitamin B12-dependent methylmalonyl pathway in Mycobacterium tuberculosis: Implications for propionate metabolism during growth on fatty acids. *J Bacteriol*. 2008. doi:10.1128/JB.01767-07

73. Griffin JE, Pandey AK, Gilmore SA, et al. Cholesterol catabolism by Mycobacterium tuberculosis requires transcriptional and metabolic adaptations. *Chem Biol*. 2012. doi:10.1016/j.chembiol.2011.12.016

74. Chiaradia L, Lefebvre C, Parra J, et al. Dissecting the mycobacterial cell envelope and defining the composition of the native mycomembrane. *Sci Rep*. 2017. doi:10.1038/s41598-017-12718-4

75. Guenin-Mace L, Simeone R, Demangel C. Lipids of Pathogenic Mycobacteria: Contributions to Virulence and Host Immune Suppression. *Transbound Emerg Dis*. 2009. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19486312.

76. Oldenburg R, Demangel C. Pathogenic and immunosuppressive properties of mycobacterial phenolic glycolipids. *Biochimie*. 2017. doi:10.1016/j.biochi.2017.03.012

77. Dulberger CL, Rubin EJ, Boutte CC. The mycobacterial cell envelope — a moving target. *Nat Rev Microbiol*. 2020. doi:10.1038/s41579-019-0273-7

78. Takayama K, Wang C, Besra GS. Pathway to synthesis and processing of mycolic acids in Mycobacterium tuberculosis. *Clin Microbiol Rev*. 2005. doi:10.1128/CMR.18.1.81-

101.2005

79. Chang Y, Fox BG. Identification of Rv3230c as the NADPH oxidoreductase of a two-protein DesA3 acyl-CoA desaturase in Mycobacterium tuberculosis H37Rv. *Biochemistry*. 2006;45(45):13476-13486. doi:10.1021/bi0615285

80. Sassetti CM, Rubin EJ. Genetic requirements for mycobacterial survival during infection. *Proc Natl Acad Sci U S A*. 2003. doi:10.1073/pnas.2134250100

81. Phetsuksiri B, Jackson M, Scherman H, et al. Unique mechanism of action of the thiourea drug isoxyl on Mycobacterium tuberculosis. *J Biol Chem*. 2003;278(52):53123-53130. doi:10.1074/jbc.M311209200

82. Singh A, Varela C, Bhatt K, et al. Identification of a Desaturase Involved in Mycolic Acid Biosynthesis in Mycobacterium smegmatis. *PLoS One*. 2016;11(10):e0164253. doi:10.1371/journal.pone.0164253

83. Quadri LEN. Biosynthesis of mycobacterial lipids by polyketide synthases and beyond. *Crit Rev Biochem Mol Biol*. 2014. doi:10.3109/10409238.2014.896859

84. Jackson M, Stadthagen G, Gicquel B. Long-chain multiple methyl-branched fatty acid-containing lipids of Mycobacterium tuberculosis: Biosynthesis, transport, regulation and biological activities. *Tuberculosis*. 2007. doi:10.1016/j.tube.2006.05.003

85. Portevin D, De Sousa-D'Auria C, Houssin C, et al. A polyketide synthase catalyzes the last condensation step of mycolic acid biosynthesis in mycobacteria and related organisms. *Proc Natl Acad Sci U S A*. 2004;101(1):314-319. doi:10.1073/pnas.0305439101

86. Portevin D, de Sousa-D'Auria C, Montrozier H, et al. The acyl-AMP ligase FadD32 and AccD4-containing acyl-CoA carboxylase are required for the synthesis of mycolic acids and essential for mycobacterial growth: identification of the carboxylation product

and determination of the acyl-CoA carboxylase componen. *J Biol Chem*. 2005;280(10):8862-8874. doi:10.1074/jbc.M408578200

87. Gao L-Y, Laval F, Lawson EH, et al. Requirement for kasB in Mycobacterium mycolic acid biosynthesis, cell wall impermeability and intracellular survival: implications for therapy. *Mol Microbiol*. 2003;49(6):1547-1563. doi:10.1046/j.1365-2958.2003.03667.x

88. Bhatt A, Kremer L, Dai AZ, Sacchettini JC, Jacobs WR. Conditional Depletion of KasA, a Key Enzyme of Mycolic Acid Biosynthesis, Leads to Mycobacterial Cell Lysis. *J Bacteriol*. 2005;187(22):7596-7606. doi:10.1128/JB.187.22.7596-7606.2005

89. Bhatt A, Fujiwara N, Bhatt K, et al. Deletion of kasB in Mycobacterium tuberculosis causes loss of acid-fastness and subclinical latent tuberculosis in immunocompetent mice. *Proc Natl Acad Sci U S A*. 2007;104(12):5157-5162. doi:10.1073/pnas.0608654104

90. Cabruja M, Mondino S, Tsai YT, Lara J, Gramajo H, Gago G. A conditional mutant of the fatty acid synthase unveils unexpected cross talks in mycobacterial lipid metabolism. *Open Biol*. 2017;7(2). doi:10.1098/rsob.160277

91. Zimhony O, Cox JS, Welch JT, Vilchèze C, Jacobs WR. Pyrazinamide inhibits the eukaryotic-like fatty acid synthetase I (FASI) of Mycobacterium tuberculosis. *Nat Med*. 2000;6(9):1043-1047. doi:10.1038/79558

92. Banerjee A, Dubnau E, Quemard A, et al. inhA, a gene encoding a target for isoniazid and ethionamide in Mycobacterium tuberculosis. *Science*. 1994;263(5144):227-230. doi:10.1126/science.8284673

93. Salzman V, Mondino S, Sala C, Cole ST, Gago G, Gramajo H. Transcriptional regulation of lipid homeostasis in mycobacteria. *Mol Microbiol*. 2010;78(1):64-77.

doi:10.1111/j.1365-2958.2010.07313.x

94. Mondino S, Gago G, Gramajo H. Transcriptional regulation of fatty acid biosynthesis in mycobacteria. *Mol Microbiol*. 2013;89(2):372-387. doi:10.1111/mmi.12282

95. Via LE, Lin PL, Ray SM, et al. Tuberculous granulomas are hypoxic in guinea pigs, rabbits, and nonhuman primates. *Infect Immun*. 2008;76(6):2333-2340. doi:10.1128/IAI.01515-07

96. Cunningham-Bussel A, Zhang T, Nathan CF. Nitrite produced by Mycobacterium tuberculosis in human macrophages in physiologic oxygen impacts bacterial ATP consumption and gene expression. *Proc Natl Acad Sci U S A*. 2013;110(45):E4256-4265. doi:10.1073/pnas.1316894110

97. Baek S-H, Li AH, Sassetti CM. Metabolic regulation of mycobacterial growth and antibiotic sensitivity. *PLoS Biol*. 2011;9(5):e1001065. doi:10.1371/journal.pbio.1001065

98. Leistikow RL, Morton RA, Bartek IL, Frimpong I, Wagner K, Voskuil MI. The Mycobacterium tuberculosis DosR regulon assists in metabolic homeostasis and enables rapid recovery from nonrespiring dormancy. *J Bacteriol*. 2010;192(6):1662-1670. doi:10.1128/JB.00926-09

99. Bagchi G, Chauhan S, Sharma D, Tyagi JS. Transcription and autoregulation of the Rv3134c-devR-devS operon of Mycobacterium tuberculosis. *Microbiology*. 2005;151(Pt 12):4045-4053. doi:10.1099/mic.0.28333-0

100. Eoh H, Wang Z, Layre E, et al. Metabolic anticipation in Mycobacterium tuberculosis. *Nat Microbiol*. 2017;2:17084. doi:10.1038/nmicrobiol.2017.84

101. Sirakova TD, Dubey VS, Deb C, et al. Identification of a diacylglycerol acyltransferase gene involved in accumulation of triacylglycerol in Mycobacterium tuberculosis under

stress. *Microbiology*. 2006;152(Pt 9):2717-2725. doi:10.1099/mic.0.28993-0

102. Vijay S, Hai HT, Thu DDA, et al. Ultrastructural Analysis of Cell Envelope and Accumulation of Lipid Inclusions in Clinical Mycobacterium tuberculosis Isolates from Sputum, Oxidative Stress, and Iron Deficiency. *Front Microbiol*. 2017;8:2681. doi:10.3389/fmicb.2017.02681

103. Daniel J, Deb C, Dubey VS, et al. Induction of a novel class of diacylglycerol acyltransferases and triacylglycerol accumulation in Mycobacterium tuberculosis as it goes into a dormancy-like state in culture. *J Bacteriol*. 2004;186(15):5017-5030. doi:10.1128/JB.186.15.5017-5030.2004

104. Galagan JE, Minch K, Peterson M, et al. The Mycobacterium tuberculosis regulatory network and hypoxia. *Nature*. 2013;499(7457):178-183. doi:10.1038/nature12337

105. Raghunandanan S, Jose L, Gopinath V, Kumar RA. Comparative label-free lipidomic analysis of Mycobacterium tuberculosis during dormancy and reactivation. *Sci Rep*. 2019;9(1):3660. doi:10.1038/s41598-019-40051-5

106. McKinney JD, Höner Zu Bentrup K, Muñoz-Elias EJ, et al. Persistence of Mycobacterium tuberculosis in macrophages and mice requires the glyoxylate shunt enzyme isocitrate lyase. *Nature*. 2000. doi:10.1038/35021074

107. Ganapathy U, Marrero J, Calhoun S, et al. Two enzymes with redundant fructose bisphosphatase activity sustain gluconeogenesis and virulence in Mycobacterium tuberculosis. *Nat Commun*. 2015;6:7912. doi:10.1038/ncomms8912

108. Del Portillo P, García-Morales L, Menéndez MC, et al. Hypoxia Is Not a Main Stress When Mycobacterium tuberculosis Is in a Dormancy-Like Long-Chain Fatty Acid Environment. *Front Cell Infect Microbiol*. 2018;8:449. doi:10.3389/fcimb.2018.00449

109. Lewis K. Persister cells. *Annu Rev Microbiol*. 2010.

doi:10.1146/annurev.micro.112408.134306

110. Russell DG, Huang L, VanderVen BC. Immunometabolism at the interface between macrophages and pathogens. *Nat Rev Immunol*. 2019;19(5):291-304. doi:10.1038/s41577-019-0124-9

111. Guilliams M, De Kleer I, Henri S, et al. Alveolar macrophages develop from fetal monocytes that differentiate into long-lived cells in the first week of life via GM-CSF. *J Exp Med*. 2013. doi:10.1084/jem.20131199

112. Tan SYS, Krasnow MA. Developmental origin of lung macrophage diversity. *Dev*. 2016. doi:10.1242/dev.129122

113. WHO. *WHO | Global Tuberculosis Report 2019*.; 2020. doi:1037//0033-2909.I26.1.78

114. Houben RMGJ, Dodd PJ. The Global Burden of Latent Tuberculosis Infection: A Re-estimation Using Mathematical Modelling. *PLoS Med*. 2016. doi:10.1371/journal.pmed.1002152

Figure legends

Figure 1: The lipid environment of Mtb in caseous TB granulomas.

Within foamy macrophages, phagosomes containing Mtb bacilli are surrounded by lipid droplets (LDs), mainly consisting of triacylglycerol (TAGs) and cholesteryl esters. Bacilli can persist extracellularly in the caseum, a lipid-rich liquid deriving from LDs released by dead foamy macrophages.

Figure 2: Reprogramming of energy metabolism upon infection with *M. tuberculosis*.

Newly infected macrophages are characterized by enhanced aerobic glycolysis, impaired oxidative phosphorylation (OXPHOS) and increased microbicidal capacity. This immunometabolic shift is triggered by activation of the TLR2/4-NF-κB signaling pathway, leading to upregulation of iNOS, IL-1β and HIF1-α. HIF1-α promotes aerobic glycolysis, which feeds a disrupted tricarboxylic acid (TCA) cycle. Breakpoints in the TCA cycle result in limited OXPHOS, accumulation of succinate (stabilizing HIF1-α) and generation of itaconate, an antimycobacterial compound. Overall, this metabolic reprogramming promotes Mtb killing through production of reactive oxygen species (ROS), nitric oxide (NO) and itaconate, catalyzed by the NADPH oxidase, inducible NO synthase (iNOS) and the immune-responsive gene 1 (IRG1), respectively. Mtb suppresses aerobic glycolysis via induction of microRNA (miR)-21 and interferon (IFN)-β, whose production is triggered by mycobacterial cell wall lipids, namely phthiocerol dimycocerosates (PDIMs).

Figure 3: Rewiring of lipid metabolism and induction of the foamy phenotype.

The foamy phenotype of macrophages is associated with lipid metabolism reprogramming: catabolic pathways (β-oxidation, TAG hydrolysis et autophagy) are inhibited while anabolic pathways are activated, leading to lipid accumulation. Mtb infection leads to activation of several signaling cascades involving Toll-Like Receptor (TLR) 2, Testicular Receptor (TR) 4 and Peroxisome Proliferator-Activated Receptor (PPAR)-γ. Mycobacterial LAM and trehalose dimycolates (TDM) induce the expression of microRNA-33, which negatively regulates FA oxidation and autophagy. Early secreted antigenic target (ESAT)-6 of Mtb induces generation of 3-hydroxybutyrate (3-HB), which is recognized by the GPR109A receptor and mediates inhibition of TAG hydrolysis. Mtb-stimulated production of pro-inflammatory cytokines also promotes LD accumulation: tumor necrosis factor (TNF)-α activates mammalian target of rapamycin complex (mTORC)-1 and the cascade of caspases, which inhibit autophagy effectors and activate lipogenic regulator SRBP (sterol regulatory element-binding protein). The interferon (IFN)-γ pathway activates hypoxia-inducible factor (HIF)-1α, enhancing the production of hypoxia-inducible gene (HIG)2 supporting LD accumulation.

Figure 4: Overview of the FA metabolism of *M. tuberculosis.*

In Mtb, FAs and free cholesterol are imported by mammalian cell entry (Mce) 1 and 4 complexes, respectively. The lipid uptake coordinator A (LucA) and the ATPase MceG are subunits shared by both transporters. Exo- and endogenous TAGs may be hydrolyzed by lipase Y (LipY). β-oxidation of fatty acyl-CoA (FA-acyl-CoA) involves the FadAB complex and generates acetyl-CoA, while cholesterol degradation mainly produces propionyl-CoA. Acetyl-CoA feeds into the TCA cycle or is alternatively assimilated by the glyoxylate shunt, involving isocitrate lyase (icl) 1 or 2. Glycolytic intermediates, such as phosphoenolpyruvate (PEP) and glucose-6-phosphate (Glu-6P) may be regenerated from oxaloacetate (OAA) by gluconeogenesis. Propionyl-CoA enters the methylcitrate cycle (MCC) or is converted into methylmalonyl-CoA, thereby fueling the TCA cycle. Acetyl-CoA may also be used for de novo *FA biosynthesis after conversion into malonyl-CoA. FA synthase I (FAS-I) catalyzes the synthesis of saturated FA (SFA), which can be converted into mono-unsaturated FAs (MUFAs)* via *the action of desaturase (Des) A3.* De novo *synthesized or imported FA can be further elongated by FAS-II to produce mycolic acids. FA may also be incorporated into TAG, phospholipids (PL) and polyketide lipids, such as phthiocerol-dimycocerosate (PDIM). These pathways involve TAG synthase (Tgs1) and several polyketide synthases (Pks), that use propionyl-CoA-derived methylmalonyl-CoA as extender unit.*

Figure 5: Immunometabolic phenotypes of macrophages in *M. tuberculosis*-infected lungs.

In Mtb-infected lungs, interstitial macrophages (IMs) are characterized by enhanced glycolysis, while pathways linked to lipid catabolism and OXPHOS are downregulated. They exhibit a pro-inflammatory profile, involving the nuclear factor (NF)-κB-mediated production of interleukin (IL)-1β, iNOS and hypoxia inducible factor (HIF)-1α. IM thus restrict Mtb growth with higher levels of NO and ROS, which stimulate the expression of stress-induced Mtb genes including the dormancy operon DosR. In contrast, alveolar macrophages (AMs) are engaged in OXPHOS, FA and lipoprotein uptake and breakdown, at the expense of glycolysis and pro-inflammatory responses. AMs are more permissive to Mtb replication and bacteria exhibit a mmarked upregulation of genes involved in cell growth and division.

Figure 1

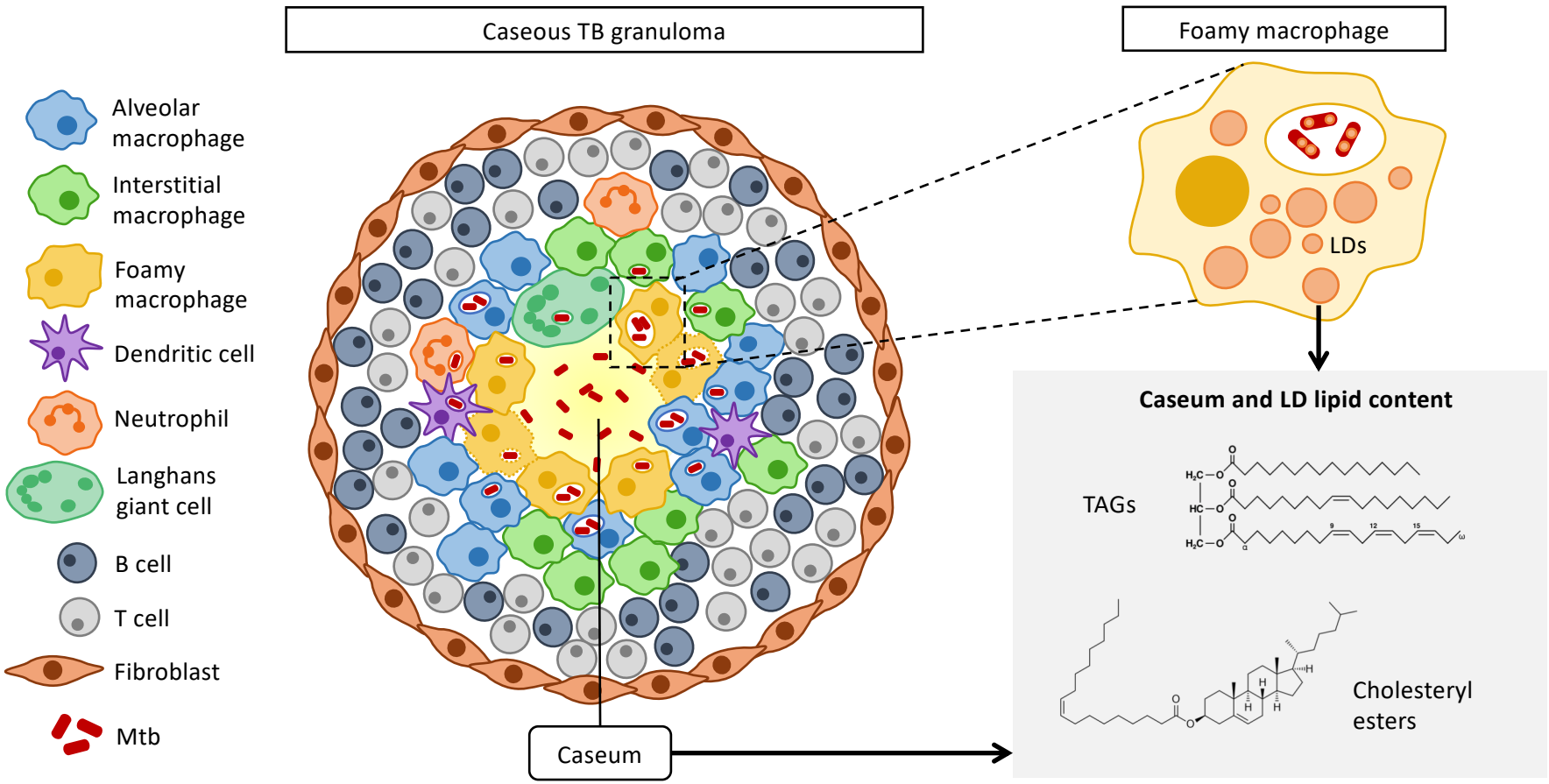

Caseous TB granuloma
Foamy macrophage
Alveolar macrophage
Interstitial macrophage
Foamy macrophage
Dendritic cell
Neutrophil
Langhans giant cell
B cell
T cell
Fibroblast
Mtb
LDs
Caseum
Caseum and LD lipid content
TAGs
Cholesteryl esters

Figure 2

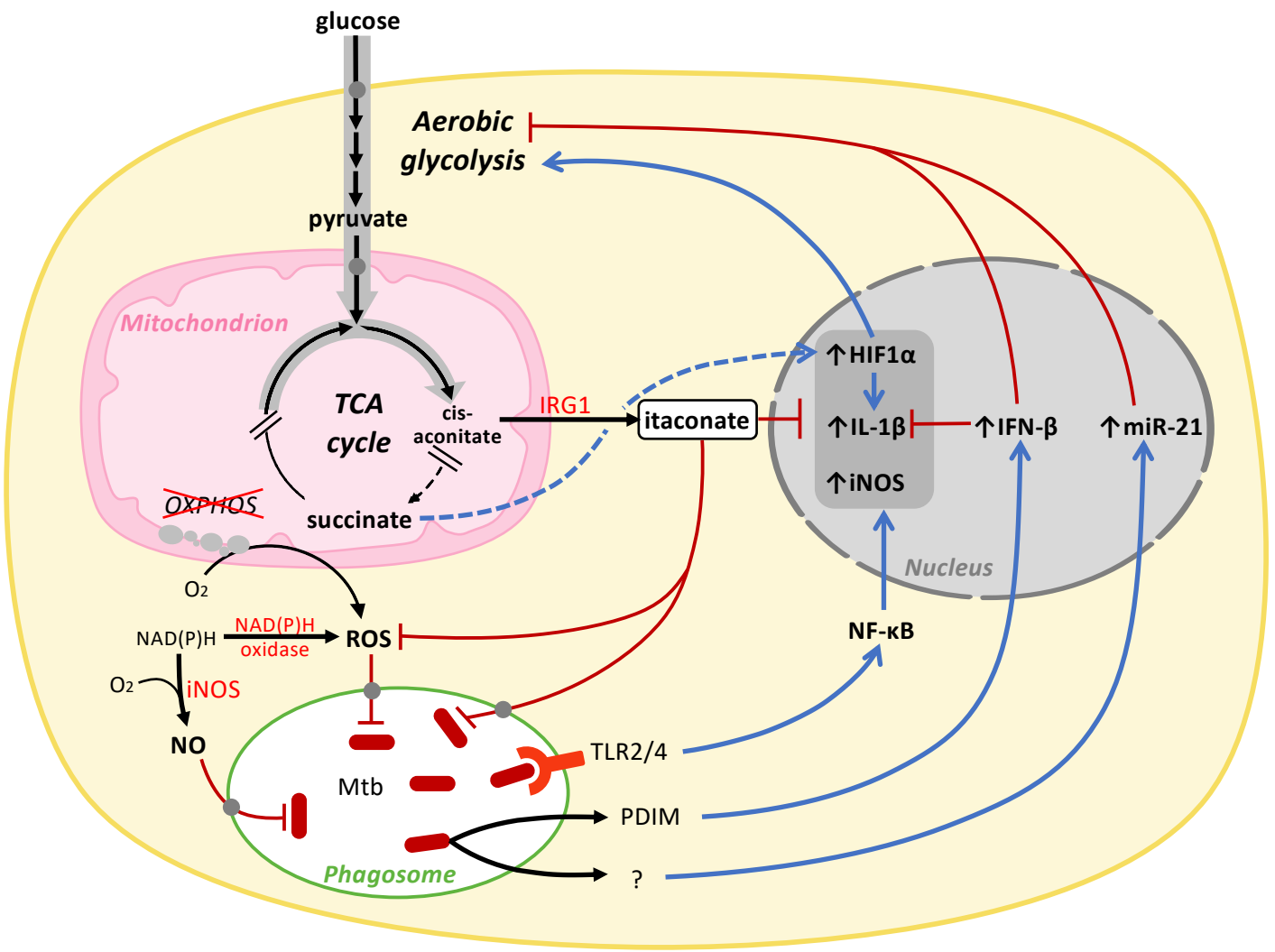
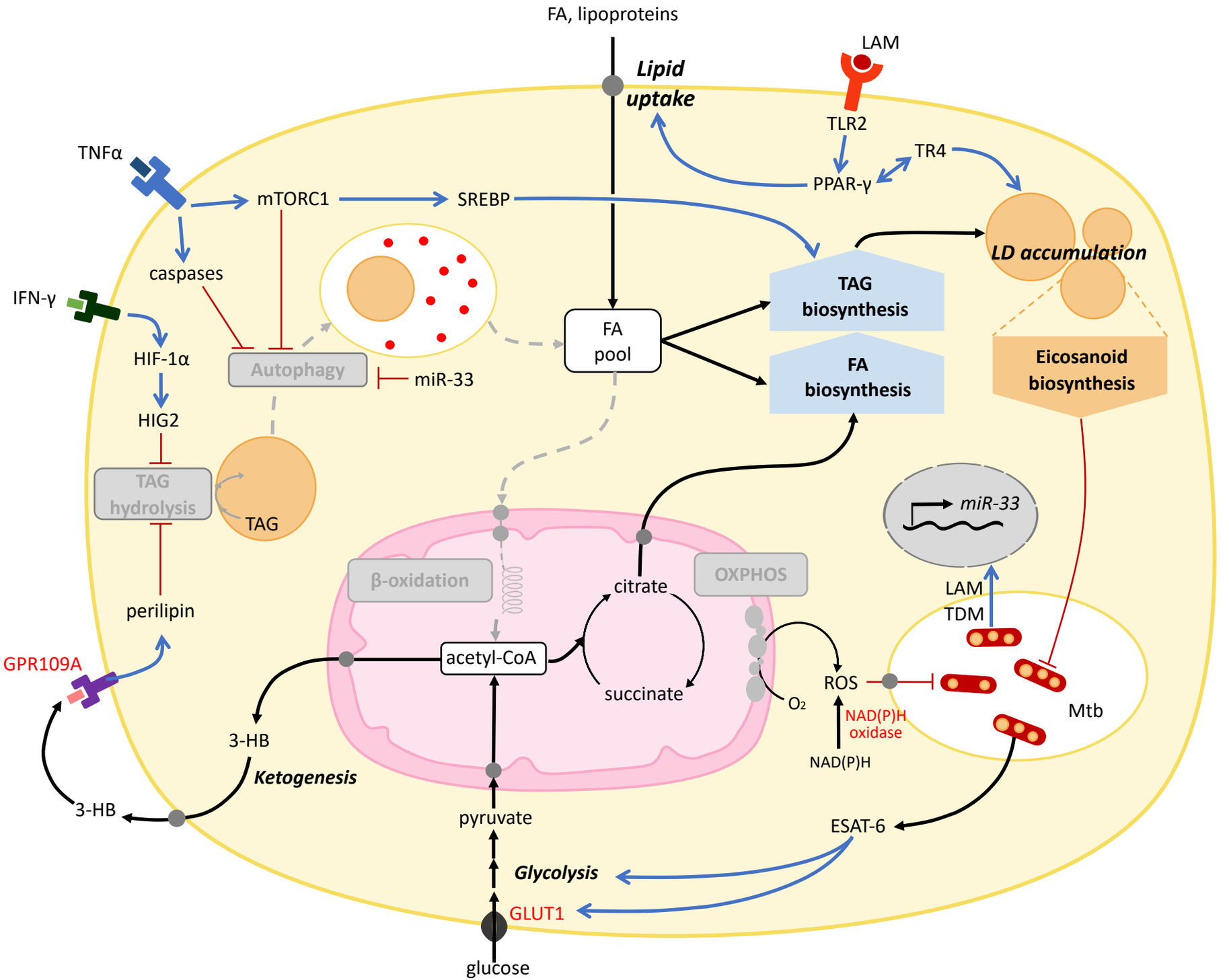
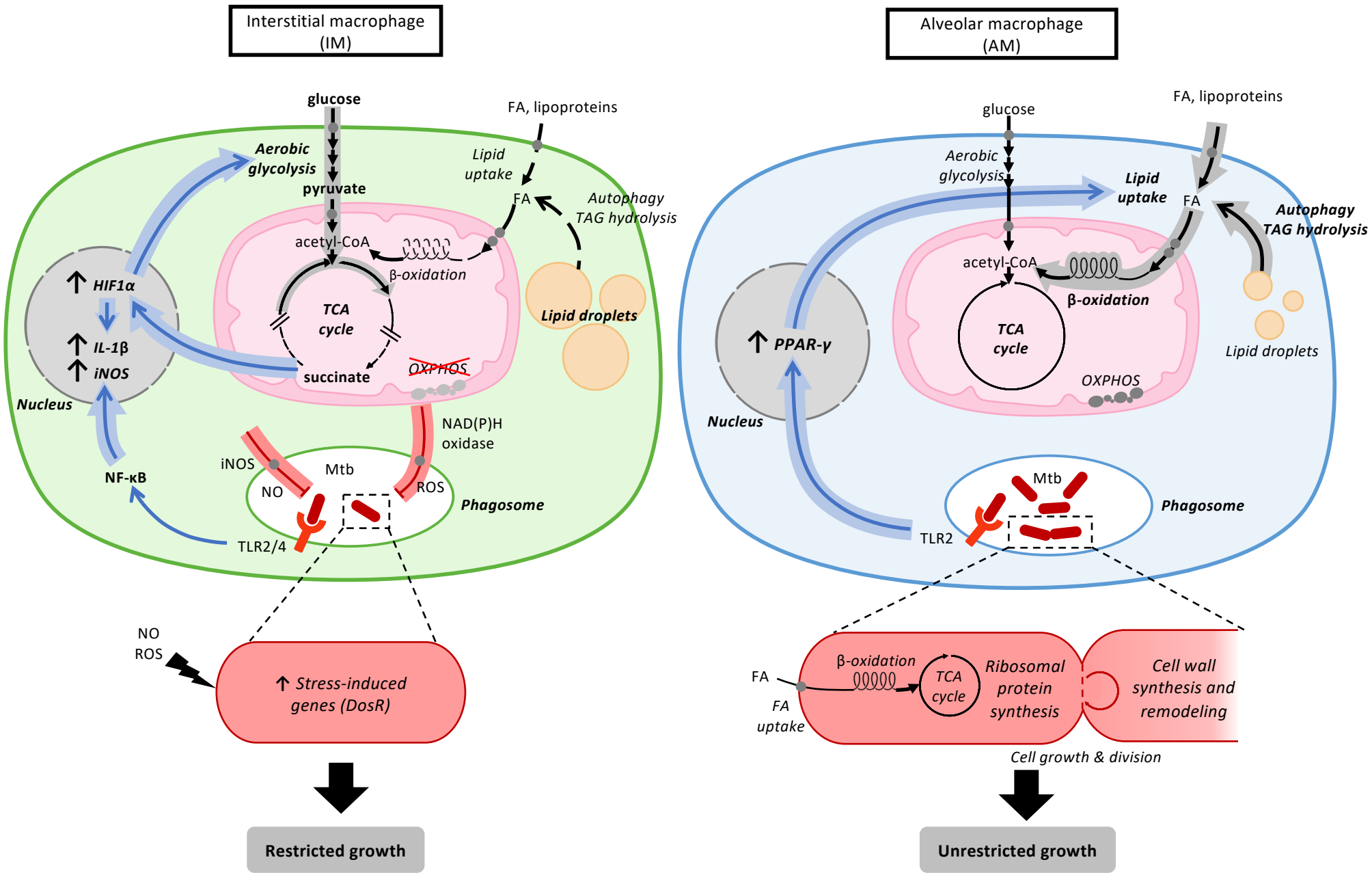

glucose
Aerobic glycolysis
pyruvate
Mitochondrion
TCA cycle
cis-aconitate
IRG1
itaconate
↑HIF1α
↑IL-1β
↑iNOS
↑IFN-β
↑miR-21
Nucleus
OXPHOS
succinate
O2
NAD(P)H
NAD(P)H oxidase
ROS
NF-κB
O2
iNOS
NO
TLR2/4
Mtb
PDIM
Phagosome
?

Figure 3


FA, lipoproteins
Lipid uptake
LAM
TLR2
TR4
PPAR-γ
TNFα
mTORC1
SREBP
caspases
IFN-γ
HIF-1α
HIG2
Autophagy
miR-33
FA pool
TAG biosynthesis
FA biosynthesis
LD accumulation
Eicosanoid biosynthesis
TAG hydrolysis
TAG
perilipin
GPR109A
β-oxidation
citrate
OXPHOS
acetyl-CoA
succinate
O2
ROS
NAD(P)H oxidase
NAD(P)H
miR-33
LAM
TDM
Mtb
3-HB
Ketogenesis
3-HB
pyruvate
ESAT-6
Glycolysis
GLUT1
glucose

glucose
Glu-6P
trehalose
Gluconeogenesis
Glycolysis
NADH
PEP
pyruvate
β-oxidation
FadAB
NADH
FA
Mce1
LucA
MceG
ATP
FA
FA-acyl-CoA
Acetyl-CoA
malonyl-CoA
LipY
LipY
TAG
TAG
OAA
citrate
MCC
TCA cycle
malate
GlcB
glyoxylate
Icl1/2
isocitrate
Methyl-isocitrate
Glyoxylate shunt
NADH
CO₂
succinyl-CoA
Icl1/2
succinate
CO₂
methylmalonyl-CoA
VitB12
cholesterol
LucA
Mce4
MceG
ATP
cholesterol
propionyl-CoA
NADH
OXPHOS
ATP
FA biosynthesis
NEFA
Mce1
ATP
FAS-I
NAD(P)H
SFA (C16-22)
DesA3
Rv3230c
MUFA
FAS-II
NAD(P)H
Tgs1
TAG
meromycolic acids (C22-62)
Desaturations
Modifications
Pks13
Carboxylation
PL
mycolic acids
trehalose
trehalose mycolates
Cell wall lipid biosynthesis
Pks
trehalose
PDIM & other polyketide lipids
Capsule
Outer membrane (mycomembrane)
Arabino-galactan
Peptido-glycan
Periplasm
Inner membrane
LM
LAM
ManLAM
Polysaccharides
Protein
Mycolic acid
Trehalose mycolates
Polyketide lipids
PDIM
PL
Glycolipids

Figure 5


Interstitial macrophage (IM)
glucose
FA, lipoproteins
Aerobic glycolysis
pyruvate
Lipid uptake
FA
Autophagy TAG hydrolysis
acetyl-CoA
β-oxidation
TCA cycle
Lipid droplets
HIF1α
IL-1β
iNOS
Nucleus
succinate
OXPHOS
NAD(P)H oxidase
iNOS
Mtb
NO
ROS
Phagosome
NF-κB
TLR2/4
NO
ROS
↑ Stress-induced genes (DosR)
Restricted growth
Alveolar macrophage (AM)
glucose
FA, lipoproteins
Aerobic glycolysis
Lipid uptake
FA
Autophagy TAG hydrolysis
acetyl-CoA
β-oxidation
TCA cycle
Lipid droplets
PPAR-γ
Nucleus
OXPHOS
Mtb
Phagosome
TLR2
FA
FA uptake
β-oxidation
TCA cycle
Ribosomal protein synthesis
Cell wall synthesis and remodeling
Cell growth & division
Unrestricted growth