PPARs and Mycobacterial Infection

Subjects: Microbiology | Biochemistry & Molecular Biology
Contributor: Koich Suzuki

The mycobacterial cell wall is composed of large amounts of lipids with varying moieties. Some mycobacteria species hijack host cells and promote lipid droplet accumulation to build the cellular environment essential for their intracellular survival. Thus, lipids are thought to be important for mycobacteria survival as well as for the invasion, parasitization, and proliferation within host cells. However, their physiological roles have not been fully elucidated. Recent studies have revealed that mycobacteria modulate the peroxisome proliferator-activated receptor (PPAR) signaling and utilize host-derived triacylglycerol (TAG) and cholesterol as both nutrient sources and evasion from the host immune system.

Keywords: mycobacteria ; M. tuberculosis ; M. leprae ; PPARs ; lipid droplets ; lipid degradaition

1. Introduction

The *Mycobacterium* genus was one of the first bacterial genera described. The most characteristic feature of mycobacteria is resistance to acid alcohol, which is utilized for Ziehl–Neelsen staining. Pathogenic mycobacteria can be categorized into three groups: *Mycobacterium tuberculosis* (*M. tuberculosis*) complex, which causes tuberculosis; *M. leprae* and *M. lepromatosis*, which both cause leprosy; and atypical mycobacteria or nontuberculous mycobacteria (NTM), which are mycobacteria responsible for a wide range of diseases. Mycobacterial cell walls consist of large amounts of lipids (30% to 40% of the total weight) that form a complex tripartite structure. The lipids are major effector molecules that affect the physiology of both the host cells and the bacilli by modulating their metabolism and stimulating immune responses to the bacilli. Most pathogenic mycobacteria, including *M. leprae*, utilize lipids from the host as a source of nutrients and to evade the immunity from the host, enabling the bacteria to both hide and replicate within host cells.

The transcription factors known as peroxisome proliferator-activated receptors (PPARs) were discovered in 1990 as enhancers of peroxisome proliferation in rodents [1] and belong to the ligand-activating nuclear hormone receptor (NR) superfamily. PPARs form heterodimers with retinoid X receptors (RXRs), enabling them to bind PPAR-responsive regulatory elements (PPRE) located in the promoter regions of their target genes. Three types of PPARs have been identified in mammals: PPAR-α (NR1C1), PPAR-β/δ (NR1C2), and PPAR-γ (NR1C3) [1][2]. Each PPAR is encoded by a separate gene and is expressed in amphibians [3], rodents [4][5], and humans [6][7]. PPAR-α and PPAR-γ are conserved proteins expressed in wide varieties of species, whereas PPAR-β/δ has diverged considerably [5]. PPARs respond to ligands and regulate the transcription of target genes. The role of PPARs is to modulate the expression of genes central to regulating glucose, lipid, and cholesterol metabolism.

2. Activation of PPARs by Mycobacteria

PPARs are activated by endogenous and exogenous compounds. For instance, eicosanoids and long-chain fatty acids (LCFAs) are the endogenous ligands for PPAR-α and PPAR-β/δ [8][9]. PPAR-γ is activated by metabolites of arachidonic acid, such as 5-oxo-eicosatetraenoic acid (5-oxo-ETE) and 5-oxo-15(S)-hydroxyeicosatetraenoic acids (5-oxo-15(S)-HETE) [10][11], in addition to oxidized low-density lipoprotein (oxLDL) derivatives [12]. Several exogenous compounds are highly specific activators and modulators for mammalian PPAR subtypes: PPAR-α by the hypolipidemic drugs clofibrate and fenofibrate and the synthetic ligand Wy-14643 and PPAR-γ by the thiazolidinedione (TZD) group of antidiabetic drugs (including rosiglitazone, ciglitazone, troglitazone, and pioglitazone) [13]. GW501516, GW0742, and bezafibrate are highly selective PPAR-β/δ agonists, while GW1929 and GW2090 are specific PPAR-γ activators [14].

PPARs are also activated by mycobacterial infection; however, the bacterial component(s) responsible are not well understood. Organisms that naturally produce unsaturated fatty acids at the C10 position are relatively rare in nature, while several mycobacteria species, including *M. vaccae*, are able to accomplish this desaturation [15][16][17][18]. The mycobacteria-derived 10 (Z)-hexadecenoic acid upregulates genes in the PPAR signaling pathway and represses the proinflammatory cytokines in macrophages [19]. Furthermore, 10 (Z)-hexadecenoic acid and monoacylglycerol (MAG), which contains 10 (Z)-hexadecenoic acid, both activate PPAR-α but have no effect on PPAR-γ or PPAR-δ. The observed

effects are blocked by PPAR-α antagonists and absent in PPAR-α-deficient mice. Recently, we found that PPAR-γ and PPAR-δ are activated in *M. leprae*-infected macrophages [20]. Infection with a recombinant strain of *M. bovis* BCG that produces phenolic glycolipid-1 (PGL-1) of *M. leprae* activates PPAR-γ in primary cultures of human Schwann cells [21].

Mannose-capped lipoarabinomannan (ManLAM) is present in the members of the *M. tuberculosis* complex, which interact with the mannose receptor (MR) in alveolar macrophages (AMs). High levels of PPAR-γ are expressed in activated AMs and macrophage-derived foam cells [22][23]. ManLAM upregulates PPAR-γ expression in human macrophages, consistent with *M. tuberculosis* infection. Furthermore, activation by ManLAM is suppressed by MR siRNA. These results indicate that the activation of PPAR-γ by *M. tuberculosis* is due to the interaction between its cell wall component ManLAM and host MRs.

Several molecules are known to bind to PPARs, including polyunsaturated fatty acids (PUFAs), such as certain ω3-PUFAs (e.g., docosahexaenoic acid with C22:6 and α-linolenic acid with C18:3) and certain ω6-PUFAs (e.g., arachidonic acid with C20:4 and linoleic acid with C18:2) [24][25]. Saturated fatty acids, such as stearic acid with C18:0 and myristic acid with C14:0, also bind to PPAR-α. *M. leprae* cell wall lipids also contain mycolic acids, other types of LCFAs typical for mycobacteria, such as alpha-mycolic acids and ketomycolic acids [26]. However, whether or not this lipid could be a ligand for PPARs is not known.

3. Emerging Roles of PPARs in Lipid Metabolism during Mycobacteria Infection

Mycobacterial infection induces lipid droplet formation in macrophages. These lipids are essential for mycobacterial survival and are presumed to be a carbon source. In several different models, *M. tuberculosis* has been shown to use accumulated lipids as a carbon source at various stages of the infectious process [27][28][29][30]. *M. tuberculosis*-induced lipid droplets in macrophages primarily contain cholesterol esters and TAG. The cholesterol is transported through the bacterial cell membrane by Mce4, a bacterial lipid transporter required for cholesterol import and its utilization [31][32]. Many of the active compounds that limit *M. tuberculosis* growth in macrophages have been found to inhibit cholesterol-related processes, indicating that cholesterol is central to *M. tuberculosis* infection [33]. Fatty acids are also an abundant lipid in human granulomas [34]. Although it has been thought that *M. tuberculosis* assimilates and metabolizes fatty acids, recent genome sequencing has identified many putative fatty acid β-oxidation genes [35].

Since *M. leprae* has lost the *mce4* operon, *M. leprae* seems to use cholesterol oxidase (ML1492) in order to convert cholesterol to cholestenone for survival [36]. In leprosy skin tissue sections, *M. leprae*-containing histiocytes and Schwann cells are filled with cholesterol [37][38]. This has been confirmed with the observation of cholesterol accumulation in *M. leprae*-infected primary macrophage [38][39]. Furthermore, the expression of cholesterol synthase, HMG-CoA reductase, was increased following infection, and when de novo cholesterol synthesis was inhibited by lovastatin, viability of *M. leprae* was reduced [39].

Conversely, high-performance thin-layer chromatography (HPTLC) analysis demonstrates that TAG is the main component of the lipid in *M. leprae*-infected human monocytic THP-1 cells [40]. It has been reported in Schwann cells that *M. leprae* infection enhances glucose uptake and stimulates the pentose phosphate pathway, which is required for TAG synthesis [41]. The accumulated TAGs are maintained by the enhanced expression of adipose differentiation-related protein (ADRP) and perilipin and by the reduced expression of hormone-sensitive lipase (HSL), which contributes to lipid degradation [42][43]. Glycerol-3-phosphate acyltransferase 3 (GPAT3) is an important rate-limiting enzyme for TAG synthesis [44]; accordingly, the internalization and viability of bacilli are lower in *GPAT3* knockout cells [40]. Furthermore, clofazimine, a therapeutic agent for leprosy, reduces the accumulation of lipid in *M. leprae*-infected THP-1 cells and promotes the production of interferon (IFN)-β and IFN-γ [45]. Therefore, mycobacterial viability is hypothesized to be closely related to lipid metabolism in host cells, especially the accumulation of TAG and cholesterol.

A recent study demonstrated that PPAR-mediated lipid metabolism is a key process in foamy cell formation following *M. leprae* infection. Among PPARs, the involvement of PPAR-γ in mycobacterial infections has been studied. Infection with *M. tuberculosis* modulates homeostasis of host lipid and induces foamy macrophages, which is necessary for intracellular parasitization and growth [46][47]. The virulent H37Rv strain of *M. tuberculosis* induces PPAR-γ expression [23], while attenuated *M. bovis* BCG slightly upregulates PPAR-γ [23][48]. In vitro interference with PPAR-γ signaling in *M. tuberculosis*-infected macrophages decreases intracellular lipid accumulation and increases mycobacterium killing [49]. Pretreatment with a PPAR-γ antagonist significantly suppressed mycobacterial (*M. bovis* BCG and *M. tuberculosis*) induction of intracellular lipid droplet accumulation [48][49][50]. In addition, *M. tuberculosis* growth was attenuated in human

lung macrophages after PPAR-γ deletion or isolation from PPAR-γ-deficient mice. Taken together, these data suggest that PPAR-γ is required for foam cell formation in tuberculous granulomas, which is related to bacilli survival.

Recently, in *M. leprae*-infected THP-1 cells, we reported that the increased expression of PPAR-γ and PPAR-δ coincided with the induction of intracellular lipid droplet formation [20]. Further, the expression of the PPAR-γ target genes *ADRP*, scavenger receptor *CD36*, fatty acid-binding protein 4 (*FABP4*), and apolipoprotein C-1 (*APOC1*) were significantly increased. Activation of the PPAR-γ signaling pathway is responsible for the upregulation of *Gpat3* expression during adipocyte differentiation [51][52][53]. We also found that GPAT3 expression is induced in THP-1 cells infected with *M. leprae*, suggesting that the mechanism of intracellular TAG accumulation is triggered by PPAR-γ activation [40].

The expression of CD36, an essential receptor for LDL-C incorporation, is also induced by *M. tuberculosis* through PPAR-γ in THP-1 macrophages [49]. CD36 can interact with surfactant in the lungs and promote the proliferation of *M. tuberculosis* in human macrophages in vitro [54]. CD36 directly interacts with TLR2 in macrophages infected with *M. bovis* BCG, as demonstrated by co-immunoprecipitation [55]. The neutralization of CD36 subsequently decreases PPAR-γ expression and lipid droplet formation and prostaglandin E2 (PGE2) secretion. In addition, *M. tuberculosis* upregulates the expression of GLUT1 and GLUT3 on the cell membrane by PPAR-γ activation of glucose metabolism. Its activation is suppressed by the PPAR-γ inhibitor T0070907 but enhanced by the agonist pioglitazone [56]. These data suggest that the activation of PPAR-γ promotes cholesterol and TAG uptake, both of which are components of the lipid droplets in mycobacteria-infected macrophages. Cholesterol accumulation in infected macrophages reduces cell wall permeability to rifampin, one of the first-line antituberculosis drugs, and masks surface antigens of mycobacteria [57]. Thus, lipids also play a role in drug resistance.

On the other hand, PPAR-α is known to promote the metabolism of lipids accumulated in *M. tuberculosis*-infected macrophages and suppress lipid droplet formation. Following infection with *M. tuberculosis*, PPAR-$\alpha^{-/-}$ bone marrow-derived macrophages decrease the activation of the transcription factor EB (TFEB), a responsible factor for the regulation of autophagy, and increase lipid droplet formation. Conversely, PPAR-α activation significantly reduces the amount of lipid droplets in mycobacteria-infected macrophages, suggesting that PPAR-α promotes lipid catabolism in mycobacterial infection [58]. Thus, PPAR-α and PPAR-γ may have opposed roles in the host defense during mycobacterial infection.

References

1. Issemann, I.; Green, S. Activation of a member of the steroid hormone receptor superfamily by peroxisome proliferators. Nature 1990, 347, 645–650.
2. Dreyer, C.; Krey, G.; Keller, H.; Givel, F.; Helftenbein, G.; Wahli, W. Control of the peroxisomal beta-oxidation pathway by a novel family of nuclear hormone receptors. Cell 1992, 68, 879–887.
3. Kawada, T. Lipid metabolism related nuclear receptor—The structure, function, expression and classification of peroxisome proliferation-activated receptor (PPAR). Nihon Rinsho 1998, 56, 1722–1728.
4. Gottlicher, M.; Widmark, E.; Li, Q.; Gustafsson, J.A. Fatty acids activate a chimera of the clofibric acid-activated receptor and the glucocorticoid receptor. Proc. Natl. Acad. Sci. USA 1992, 89, 4653–4657.
5. Kliewer, S.A.; Forman, B.M.; Blumberg, B.; Ong, E.S.; Borgmeyer, U.; Mangelsdorf, D.J.; Umesono, K.; Evans, R.M. Differential expression and activation of a family of murine peroxisome proliferator-activated receptors. Proc. Natl. Acad. Sci. USA 1994, 91, 7355–7359.
6. Greene, M.E.; Blumberg, B.; McBride, O.W.; Yi, H.F.; Kronquist, K.; Kwan, K.; Hsieh, L.; Greene, G.; Nimer, S.D. Isolation of the human peroxisome proliferator activated receptor gamma cDNA: Expression in hematopoietic cells and chromosomal mapping. Gene Expr. 1995, 4, 281–299.
7. Sher, T.; Yi, H.F.; McBride, O.W.; Gonzalez, F.J. cDNA cloning, chromosomal mapping, and functional characterization of the human peroxisome proliferator activated receptor. Biochemistry 1993, 32, 5598–5604.
8. Yu, K.; Bayona, W.; Kallen, C.B.; Harding, H.P.; Ravera, C.P.; McMahon, G.; Brown, M.; Lazar, M.A. Differential activation of peroxisome proliferator-activated receptors by eicosanoids. J. Biol. Chem. 1995, 270, 23975–23983.
9. Narala, V.R.; Adapala, R.K.; Suresh, M.V.; Brock, T.G.; Peters-Golden, M.; Reddy, R.C. Leukotriene B4 is a physiologically relevant endogenous peroxisome proliferator-activated receptor-alpha agonist. J. Biol. Chem. 2010, 285, 22067–22074.
10. O'Flaherty, J.T.; Rogers, L.C.; Paumi, C.M.; Hantgan, R.R.; Thomas, L.R.; Clay, C.E.; High, K.; Chen, Y.Q.; Willingham, M.C.; Smitherman, P.K.; et al. 5-Oxo-ETE analogs and the proliferation of cancer cells. Biochim. Biophys. Acta 2005,

1736, 228–236.

11. Altmann, R.; Hausmann, M.; Spottl, T.; Gruber, M.; Bull, A.W.; Menzel, K.; Vogl, D.; Herfarth, H.; Scholmerich, J.; Falk, W.; et al. 13-Oxo-ODE is an endogenous ligand for PPARgamma in human colonic epithelial cells. Biochem. Pharmacol. 2007, 74, 612–622.
12. Tontonoz, P.; Nagy, L.; Alvarez, J.G.; Thomazy, V.A.; Evans, R.M. PPARgamma promotes monocyte/macrophage differentiation and uptake of oxidized LDL. Cell 1998, 93, 241–252.
13. Yki-Jarvinen, H. Thiazolidinediones. N. Engl. J. Med. 2004, 351, 1106–1118.
14. Marion-Letellier, R.; Savoye, G.; Ghosh, S. Fatty acids, eicosanoids and PPAR gamma. Eur. J. Pharmacol. 2016, 785, 44–49.
15. Suutari, M.; Laakso, S. Effect of growth temperature on the fatty acid composition of Mycobacterium phlei. Arch. Microbiol. 1993, 159, 119–123.
16. Springer, B.; Kirschner, P.; Rost-Meyer, G.; Schroder, K.H.; Kroppenstedt, R.M.; Bottger, E.C. Mycobacterium interjectum, a new species isolated from a patient with chronic lymphadenitis. J. Clin. Microbiol. 1993, 31, 3083–3089.
17. Pacifico, C.; Fernandes, P.; de Carvalho, C. Mycobacterial response to organic solvents and possible implications on cross-resistance with antimicrobial agents. Front. Microbiol. 2018, 9, 1–12.
18. Chou, S.; Chedore, P.; Kasatiya, S. Use of gas chromatographic fatty acid and mycolic acid cleavage product determination to differentiate among Mycobacterium genavense, Mycobacterium fortuitum, Mycobacterium simiae, and Mycobacterium tuberculosis. J. Clin. Microbiol. 1998, 36, 577–579.
19. Smith, D.G.; Martinelli, R.; Besra, G.S.; Illarionov, P.A.; Szatmari, I.; Brazda, P.; Allen, M.A.; Xu, W.; Wang, X.; Nagy, L.; et al. Identification and characterization of a novel anti-inflammatory lipid isolated from Mycobacterium vaccae, a soil-derived bacterium with immunoregulatory and stress resilience properties. Psychopharmacology 2019, 236, 1653–1670.
20. Luo, Y.; Tanigawa, K.; Kawashima, A.; Ishido, Y.; Ishii, N.; Suzuki, K. The function of peroxisome proliferator-activated receptors PPAR-gamma and PPAR-delta in Mycobacterium leprae-induced foam cell formation in host macrophages. PLoS Negl. Trop. Dis. 2020, 14, e0008850.
21. Diaz Acosta, C.C.; Dias, A.A.; Rosa, T.; Batista-Silva, L.R.; Rosa, P.S.; Toledo-Pinto, T.G.; Costa, F.; Lara, F.A.; Rodrigues, L.S.; Mattos, K.A.; et al. PGL I expression in live bacteria allows activation of a CD206/PPARgamma cross-talk that may contribute to successful Mycobacterium leprae colonization of peripheral nerves. PLoS Pathog. 2018, 14, e1007151.
22. Arnett, E.; Weaver, A.M.; Woodyard, K.C.; Montoya, M.J.; Li, M.; Hoang, K.V.; Hayhurst, A.; Azad, A.K.; Schlesinger, L.S. PPARgamma is critical for Mycobacterium tuberculosis induction of Mcl-1 and limitation of human macrophage apoptosis. PLoS Pathog. 2018, 14, e1007100.
23. Rajaram, M.V.; Brooks, M.N.; Morris, J.D.; Torrelles, J.B.; Azad, A.K.; Schlesinger, L.S. Mycobacterium tuberculosis activates human macrophage peroxisome proliferator-activated receptor gamma linking mannose receptor recognition to regulation of immune responses. J. Immunol. 2010, 185, 929–942.
24. Luo, W.; Xu, Q.; Wang, Q.; Wu, H.; Hua, J. Effect of modulation of PPAR-gamma activity on Kupffer cells M1/M2 polarization in the development of non-alcoholic fatty liver disease. Sci. Rep. 2017, 7, 44612.
25. Lian, M.; Luo, W.; Sui, Y.; Li, Z.; Hua, J. Dietary n-3 PUFA protects mice from con A induced liver injury by modulating regulatory T cells and PPAR-gamma expression. PLoS ONE 2015, 10, e0132741.
26. Minnikin, D.E.; Dobson, G.; Goodfellow, M.; Draper, P.; Magnusson, M. Quantitative comparison of the mycolic and fatty acid compositions of Mycobacterium leprae and Mycobacterium gordonae. J. Gen. Microbiol. 1985, 131, 2013–2021.
27. Gouzy, A.; Larrouy-Maumus, G.; Wu, T.D.; Peixoto, A.; Levillain, F.; Lugo-Villarino, G.; Guerquin-Kern, J.L.; de Carvalho, L.P.; Poquet, Y.; Neyrolles, O. Mycobacterium tuberculosis nitrogen assimilation and host colonization require aspartate. Nat. Chem. Biol. 2013, 9, 674–676.
28. Trujillo, C.; Blumenthal, A.; Marrero, J.; Rhee, K.Y.; Schnappinger, D.; Ehrt, S. Triosephosphate isomerase is dispensable in vitro yet essential for Mycobacterium tuberculosis to establish infection. mBio 2014, 5, e00085.
29. Daniel, J.; Maamar, H.; Deb, C.; Sirakova, T.D.; Kolattukudy, P.E. Mycobacterium tuberculosis uses host triacylglycerol to accumulate lipid droplets and acquires a dormancy-like phenotype in lipid-loaded macrophages. PLoS Pathog. 2011, 7, e1002093.
30. Griffin, J.E.; Gawronski, J.D.; Dejesus, M.A.; Ioerger, T.R.; Akerley, B.J.; Sassetti, C.M. High-resolution phenotypic profiling defines genes essential for mycobacterial growth and cholesterol catabolism. PLoS Pathog. 2011, 7,

e1002251.

31. Pandey, A.K.; Sassetti, C.M. Mycobacterial persistence requires the utilization of host cholesterol. Proc. Natl. Acad. Sci. USA 2008, 105, 4376–4380.
32. Griffin, J.E.; Pandey, A.K.; Gilmore, S.A.; Mizrahi, V.; McKinney, J.D.; Bertozzi, C.R.; Sassetti, C.M. Cholesterol catabolism by Mycobacterium tuberculosis requires transcriptional and metabolic adaptations. Chem. Biol. 2012, 19, 218–227.
33. VanderVen, B.C.; Fahey, R.J.; Lee, W.; Liu, Y.; Abramovitch, R.B.; Memmott, C.; Crowe, A.M.; Eltis, L.D.; Perola, E.; Deininger, D.D.; 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, e1004679.
34. Kim, M.J.; Wainwright, H.C.; Locketz, M.; Bekker, L.G.; Walther, G.B.; Dittrich, C.; Visser, A.; Wang, W.; Hsu, F.F.; Wiehart, U.; et al. Caseation of human tuberculosis granulomas correlates with elevated host lipid metabolism. EMBO Mol. Med. 2010, 2, 258–274.
35. Cole, S.T.; Brosch, R.; Parkhill, J.; Garnier, T.; Churcher, C.; Harris, D.; Gordon, S.V.; Eiglmeier, K.; Gas, S.; Barry, C.E., 3rd; et al. Deciphering the biology of Mycobacterium tuberculosis from the complete genome sequence. Nature 1998, 393, 537–544.
36. Marques, M.A.; Berredo-Pinho, M.; Rosa, T.L.; Pujari, V.; Lemes, R.M.; Lery, L.M.; Silva, C.A.; Guimaraes, A.C.; Atella, G.C.; Wheat, W.H.; et al. The essential role of cholesterol metabolism in the intracellular survival of Mycobacterium leprae is not coupled to central carbon metabolism and energy production. J. Bacteriol. 2015, 197, 3698–3707.
37. Chatterjee, K.R.; Das Gupta, N.N.; De, M.L. Electron microscopic observations on the morphology of Mycobacterium leprae. Exp. Cell Res. 1959, 18, 521–527.
38. Mattos, K.A.; Lara, F.A.; Oliveira, V.G.; Rodrigues, L.S.; D'Avila, H.; Melo, R.C.; Manso, P.P.; Sarno, E.N.; Bozza, P.T.; Pessolani, M.C. Modulation of lipid droplets by Mycobacterium leprae in Schwann cells: A putative mechanism for host lipid acquisition and bacterial survival in phagosomes. Cell Microbiol. 2011, 13, 259–273.
39. Mattos, K.A.; Oliveira, V.C.; Berredo-Pinho, M.; Amaral, J.J.; Antunes, L.C.; Melo, R.C.; Acosta, C.C.; Moura, D.F.; Olmo, R.; Han, J.; et al. Mycobacterium leprae intracellular survival relies on cholesterol accumulation in infected macrophages: A potential target for new drugs for leprosy treatment. Cell Microbiol. 2014, 16, 797–815.
40. Tanigawa, K.; Hayashi, Y.; Hama, K.; Yamashita, A.; Yokoyama, K.; Luo, Y.; Kawashima, A.; Maeda, Y.; Nakamura, Y.; Harada, A.; et al. Mycobacterium leprae promotes triacylglycerol de novo synthesis through induction of GPAT3 expression in human premonocytic THP-1 cells. PLoS ONE 2021, 16, e0249184.
41. Medeiros, R.C.; Girardi, K.D.; Cardoso, F.K.; Mietto, B.S.; Pinto, T.G.; Gomez, L.S.; Rodrigues, L.S.; Gandini, M.; Amaral, J.J.; Antunes, S.L.; et al. Subversion of schwann cell glucose metabolism by Mycobacterium leprae. J. Biol. Chem. 2016, 291, 21375–21387.
42. Tanigawa, K.; Degang, Y.; Kawashima, A.; Akama, T.; Yoshihara, A.; Ishido, Y.; Makino, M.; Ishii, N.; Suzuki, K. Essential role of hormone-sensitive lipase (HSL) in the maintenance of lipid storage in Mycobacterium leprae-infected macrophages. Microb. Pathog. 2012, 52, 285–291.
43. Tanigawa, K.; Suzuki, K.; Nakamura, K.; Akama, T.; Kawashima, A.; Wu, H.; Hayashi, M.; Takahashi, S.; Ikuyama, S.; Ito, T.; et al. Expression of adipose differentiation-related protein (ADRP) and perilipin in macrophages infected with Mycobacterium leprae. FEMS Microbiol. Lett. 2008, 289, 72–79.
44. Karasawa, K.; Tanigawa, K.; Harada, A.; Yamashita, A. Transcriptional Regulation of Acyl-CoA:Glycerol-sn-3-Phosphate Acyltransferases. Int. J. Mol. Sci. 2019, 20, 964.
45. Degang, Y.; Akama, T.; Hara, T.; Tanigawa, K.; Ishido, Y.; Gidoh, M.; Makino, M.; Ishii, N.; Suzuki, K. Clofazimine modulates the expression of lipid metabolism proteins in Mycobacterium leprae-infected macrophages. PLoS Negl. Trop. Dis. 2012, 6, e1936.
46. Peyron, P.; Vaubourgeix, J.; Poquet, Y.; Levillain, F.; Botanch, C.; Bardou, F.; Daffe, M.; Emile, J.F.; Marchou, B.; Cardona, P.J.; et al. Foamy macrophages from tuberculous patients' granulomas constitute a nutrient-rich reservoir for M. tuberculosis persistence. PLoS Pathog. 2008, 4, e1000204.
47. Singh, V.; Jamwal, S.; Jain, R.; Verma, P.; Gokhale, R.; Rao, K.V. Mycobacterium tuberculosis-driven targeted recalibration of macrophage lipid homeostasis promotes the foamy phenotype. Cell Host Microbe 2012, 12, 669–681.
48. Almeida, P.E.; Silva, A.R.; Maya-Monteiro, C.M.; Torocsik, D.; D'Avila, H.; Dezso, B.; Magalhaes, K.G.; Castro-Faria-Neto, H.C.; Nagy, L.; Bozza, P.T. Mycobacterium bovis bacillus Calmette-Guerin infection induces TLR2-dependent peroxisome proliferator-activated receptor gamma expression and activation: Functions in inflammation, lipid metabolism, and pathogenesis. J. Immunol. 2009, 183, 1337–1345.

49. Mahajan, S.; Dkhar, H.K.; Chandra, V.; Dave, S.; Nanduri, R.; Janmeja, A.K.; Agrewala, J.N.; Gupta, P. Mycobacterium tuberculosis modulates macrophage lipid-sensing nuclear receptors PPARgamma and TR4 for survival. J. Immunol. 2012, 188, 5593–5603.
50. D’Avila, H.; Melo, R.C.; Parreira, G.G.; Werneck-Barroso, E.; Castro-Faria-Neto, H.C.; Bozza, P.T. Mycobacterium bovis bacillus Calmette-Guerin induces TLR2-mediated formation of lipid bodies: Intracellular domains for eicosanoid synthesis in vivo. J. Immunol. 2006, 176, 3087–3097.
51. Cao, J.; Li, J.L.; Li, D.; Tobin, J.F.; Gimeno, R.E. Molecular identification of microsomal acyl-CoA:glycerol-3-phosphate acyltransferase, a key enzyme in de novo triacylglycerol synthesis. Proc. Natl. Acad. Sci. USA 2006, 103, 19695–19700.
52. Gorga, A.; Rindone, G.M.; Regueira, M.; Pellizzari, E.H.; Camberos, M.C.; Cigorraga, S.B.; Riera, M.F.; Galardo, M.N.; Meroni, S.B. PPARgamma activation regulates lipid droplet formation and lactate production in rat Sertoli cells. Cell Tissue Res. 2017, 369, 611–624.
53. Lee, M.J.; Jash, S.; Jones, J.E.C.; Puri, V.; Fried, S.K. Rosiglitazone remodels the lipid droplet and britens human visceral and subcutaneous adipocytes ex vivo. J. Lipid Res. 2019, 60, 856–868.
54. Dodd, C.E.; Pyle, C.J.; Glowinski, R.; Rajaram, M.V.; Schlesinger, L.S. CD36-Mediated Uptake of Surfactant Lipids by Human Macrophages Promotes Intracellular Growth of Mycobacterium tuberculosis. J. Immunol. 2016, 197, 4727–4735.
55. Almeida, P.E.; Roque, N.R.; Magalhaes, K.G.; Mattos, K.A.; Teixeira, L.; Maya-Monteiro, C.; Almeida, C.J.; Castro-Faria-Neto, H.C.; Ryffel, B.; Quesniaux, V.F.; et al. Differential TLR2 downstream signaling regulates lipid metabolism and cytokine production triggered by Mycobacterium bovis BCG infection. Biochim. Biophys. Acta 2014, 1841, 97–107.
56. Dasgupta, S.; Rai, R.C. PPAR-gamma and Akt regulate GLUT1 and GLUT3 surface localization during Mycobacterium tuberculosis infection. Mol. Cell Biochem. 2018, 440, 127–138.
57. Brzostek, A.; Pawelczyk, J.; Rumijowska-Galewicz, A.; Dziadek, B.; Dziadek, J. Mycobacterium tuberculosis is able to accumulate and utilize cholesterol. J. Bacteriol. 2009, 191, 6584–6591.
58. Kim, Y.S.; Lee, H.M.; Kim, J.K.; Yang, C.S.; Kim, T.S.; Jung, M.; Jin, H.S.; Kim, S.; Jang, J.; Oh, G.T.; et al. PPAR-alpha Activation Mediates Innate Host Defense through Induction of TFEB and Lipid Catabolism. J. Immunol. 2017, 198, 3283–3295.