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Macrophage immunoregulatory pathways in tuberculosis

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Abstract

Macrophages, the major host cells harboring *Mycobacterium tuberculosis (M.tb)*, are a heterogeneous cell type depending on their tissue of origin and host they are derived from. Significant discord in macrophage responses to *M.tb* exists due to differences in *M.tb* strains and the various types of macrophages used to study tuberculosis (TB). This review will summarize current concepts regarding macrophage responses to *M.tb* infection, while pointing out relevant differences in experimental outcomes due to the use of divergent model systems. A brief description of the lung environment is included since there is increasing evidence that the alveolar macrophage (AM) has immunoregulatory properties that can delay optimal protective host immune responses. In this context, this review focuses on selected macrophage immunoregulatory pattern recognition receptors (PRRs), cytokines, negative regulators of inflammation, lipid mediators and microRNAs (miRNAs).

Keywords

macrophages; innate immunity; pattern recognition receptors; microRNAs; lung

1. Introduction

Macrophages serve as the major host cell niche for intracellular growth and persistence of *M.tb* during all phases of TB, from primary infection with bacillary dissemination, through latency (with bacterial persistence within granulomas) and reactivation TB. In addition, macrophages are responsible for activation of protective immune responses, both innate and acquired, thus playing a critical role in the ongoing cross-talk that is necessary to control or eliminate the infection [1-6].

Our understanding of the great heterogeneity and plasticity of macrophages residing in diverse tissues of different mammals continues to evolve [7-10]. If our goal of finding relevant tissue bio-signatures and therapeutic targets to combat human *M.tb* is to be

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achieved, we must pay particular attention to the stage of TB infection being modeled (e.g. primary infection, latency with bacterial persistence, reactivation), source of the macrophage (*e.g.* primary or cell line, human, or other mammal), and experimental conditions, particularly as they apply to the specific tissue microenvironment being modeled (e.g. media for *in vitro* studies, organ for *in vivo* studies, granuloma).

In this review, we will summarize current concepts in macrophage biology as they pertain to *M.tb* pathogenesis. We place the discussion in the context of lung biology and alveolar macrophages (AMs), given their prominent role in airborne TB. AMs are unique mucosal immunoregulatory cells and there is increasing evidence that they are important in allowing *M.tb* to replicate for an extended period of time prior to complete activation of protective immune responses [11-16]. We have coined the time period necessary for optimal responses to occur in the lung "the switching time" [11] and provide evidence that *M.tb* itself can further drive the immunoregulatory activation state of macrophages to enhance its survival [12]. Thus we highlight emerging key macrophage immunoregulatory determinants for *M.tb*.

2. Airborne *M.tb* infection and the lung

M.tb nearly always infects humans via inhalation of airborne droplets released by individuals with active TB that are deposited in the lung alveolus, where as few as one to five bacteria can result in infection. Deposited *M.tb* are engulfed by the resident AMs, which are less able to kill and clear all of the bacteria, ultimately becoming the microbe's home and allowing for dissemination to occur. Primary *M.tb* infection is generally self-limited (subclinical), most often resulting in latency and containment of the bacteria that were not eradicated, although complete clearance is possible. During primary infection bacteremia can occur, resulting in bacterial deposition in other organs which serve as a nidus for extrapulmonary reactivation later [17].

Fourteen thousand liters of inhaled air passes through the nose, mouth and trachea each day, where mechanical defenses clear particulates and microbes ≥ 5um in diameter. Smaller inhaled items may pass through the bronchioles and settle in the alveoli where they encounter AMs. The alveoli are delicate grape-like clusters which exchange gases with the surrounding capillary meshwork [18]. Due to the fragility of alveoli and the need for gas exchange, clearance of pathogenic matter without excessive and destructive inflammation is extremely important in this locale.

2.1. Alveolar physiology and cell types

A thin lining of epithelial type I and type II cells surrounds the alveolus. Type I cells are thin, flat and cover 93-97% of the alveolar surface, allowing for efficient gas exchange. Type II epithelial cells are cuboidal with apical microvilli and cytoplasmic lamellar bodies. They produce and secrete pulmonary surfactant lipids and proteins as well as other soluble components of the innate immune system [19]. These substances have widespread immune activity, functioning as opsonins and/or microbial aggregating agents, signaling molecules that shape immune cell phenotypes and microbicides that destroy or destabilize microbial cell walls [20-32]. In addition to AMs, and the epithelium and interstitium which contain

capillaries and venules, there are several other innate immune cells including intravascular and interstitial macrophages (IMs), dendritic cells (DCs) and scattered neutrophils [33,34].

2.2. Surfactant Proteins and hydrolases

Pulmonary surfactant is a lipid and protein complex which forms a thin film at the air-liquid alveolar interface for the purpose of reducing surface tension and preventing alveolar collapse during expiration. AMs are bathed in surfactant which is primarily composed of phospholipids such as dipalmitoyl phosphatidylcholine (DPPC) with lesser concentrations of other lipids and cholesterol [35]. There are four surfactant associated proteins, Surfactant protein -A (SP-A), SP-B, SP-C and SP-D. Surfactant lipids adsorb to the air-liquid interface with the assistance of SP-B and SP-C [reviewed in [36, 37]. SP-A and SP-D are large, multimeric and relatively hydrophilic collagenous lectins (collectins) with carbohydrate recognition domains (CRDs) that are important in the Ca^{2+}-dependent recognition of microbes [reviewed in [37]. SP-A and SP-D are key regulators in the pulmonary innate immune response through several mechanisms including microbe binding, agglutination, and direct effects on immune cells [38].

SP-A enhances macrophage phagocytosis of apoptotic cells and various pathogens including *M.tb* [39-43] through direct interaction with macrophages [44] as well as binding to the bacterial cell wall proteins and lipoglycans [45,46]. SP-A is a major regulator of macrophage phenotype and function with effects on PRRs, the oxidative burst, and negative regulators of inflammation [21,47-49]. By interacting with mannosylated lipoarabinomannan (ManLAM) found on virulent *M.tb* (and some other pathogenic mycobacteria) [22], SP-D agglutinates *M.tb* and decreases macrophage phagocytosis while enhancing phagolysosomal fusion and killing of the bacilli that are phagocytosed [22,23,50]. Type II cells produce lamellar bodies which are packed with surfactant phospholipids and hydrolytic enzymes and hydrolases in the extracellular lining of the lung [51,52]. Hydrolases can alter the outer cell wall of *M.tb* with the potential to change the macrophage-microbe interaction and host immune response [20].

3. Macrophage phenotype and functional diversity

Macrophages are phenotypically heterogeneous, having diverse functions in different tissues. Some studies indicate that the initial interaction of macrophages with specific cytokines determines their functional phenotype, while others have shown that macrophages can be continuously altered as the environment changes [53-55]. Macrophage heterogeneity has a direct impact on *M.tb* interactions in different tissue environments. Macrophages have been categorized into two major groups: the pro-inflammatory, “classically” activated M1 type macrophage and the immunoregulatory, “alternatively” activated M2 type macrophage [56,57]. However, it is increasingly clear that macrophage function represents a spectrum, with biological activities varying greatly among mammalian species and experimental stimuli [7,58-65]. For example, mouse macrophages express unique phenotypic markers for M1/M2, not expressed by human macrophages [57,61].

3.1. Classically activated macrophage (CAM)

Once primed by IFNγ, followed by a second signal such as TNFα or LPS, the CAM mediates more efficient antigen presentation, increased synthesis and release of pro-inflammatory mediators and more efficient phagocytosis [57]. One of the most reliable markers of mouse CAMs is robust nitric oxide (NO) production; however, human macrophages produce limited NO even after activation [66], an observation which holds relevance for TB research, discussed below.

3.2. Alternatively activate macrophages (AAMs)

AAMs are generated by IL-4, and IL-13, which are produced by T helper 2 (Th2) cells, and partially share receptor complexes [67]. AAMs generally mediate Th2 type immune responses [57]. In antithesis to CAMs, AAMs are generally anti-inflammatory, producing high levels of IL-10 and TGF-β and are less efficient antigen presenting cells due to reduced MHC class II expression [56,57,60]. AAMs also demonstrate impaired killing of intracellular pathogens, but play an important role in controlling extracellular parasites [68]. In general, AAMs are believed to promote resolution of inflammation and wound healing. The impact of these types of macrophages in TB pathogenesis is being increasingly realized [11-16,69].

3.3. AMs

AMs reside beneath the surfactant monolayer on the luminal side of the alveolar epithelial cells and are a first line of immune cell defense in the alveolus (Fig. 1). It is estimated that there are 8-12 AMs per alveolus [70-72] , which through irradiation studies, were determined to originate from blood monocyte precursors [73]. Following differentiation in the lung, resident AMs are relatively long lived, with a turnover rate of around 40% of the population per year [74]. However, there is also evidence in mice for local production of macrophages from stem cells [75].

AMs are uniquely adapted to functioning in the alveolar environment, where they act as sentinels against invading organisms but also serve to limit inflammation and minimize lung injury to preserve alveolar function. AM activation is tightly regulated and involves a complex balancing act between activating and repressing signals. On the one hand, PRRs like Toll-like Receptors (TLRs) recognize pathogen associated molecular patterns (PAMPs) and initiate inflammatory responses, while receptors for inflammatory cytokines such as TNFα, IL-1β and IFN-γ perpetuate inflammation [7]. On the other hand, signaling through IL-10 and TGFβ, as well as non-TLR PRRs such as the mannose receptor (MR, CD206) limit the progression of inflammation [7]. Negative regulation of inflammation is also achieved by cell-to-cell interactions, via epithelial cell ligation of AM receptors such as CD200 Receptor (CD200R) [76], triggering receptor expressed by myeloid cells 2 (TREM2) [77,78] and signal-regulatory protein-α (SIRP-α) [79]. AMs control inflammation by suppressing the induction of innate and adaptive immunity through decreased antigen presentation, limited oxidant production, and enhanced release of anti-inflammatory cytokines [7,80]. AMs from healthy human donors make low levels of O_2 metabolites when compared to neutrophils or PBMCs following stimulation [80-82] and there is no detectable oxidative burst following *M.tb* infection of MDMs [23]. The lack of robust oxidative

responses in human AMs and MDMs are an important contrast to the substantial evidence for a protective role of ROIs and NO for elimination of *M.tb* in the murine model of infection [83-88]. AMs are ineffective APCs [80], which delays and limits the initiation of T cell inflammatory responses [7]. In concert, CD28 co-stimulation is defective in AMs [89] and the APC ability of DCs *in vitro* and *in vivo* and can be inhibited by AMs [90].

Due to the unique, intermediate phenotype exhibited by AMs (Fig. 2), the conventional categorization of CAM versus AAM does not hold [7]. In accordance with their distinct role in maintaining lung homeostasis, our group has designated AMs as "immunoregulatory macrophages". Additional efforts in characterizing AMs are required, particularly in regard to human AMs.

3.4. Intravascular and interstitial macrophages (IMs)

Intravascular and interstitial macrophages (IMs) differ in location and function from AMs. IMs are believed to function in regulating tissue fibrosis, inflammation, and antigen presentation [91] whereas intravascular macrophages function in the cross talk between APCs in the lung interstitium for recruiting neutrophils or myeloid cells [92]. The existence of lung macrophage subsets with different functional properties requires additional exploration to better understand their contributions to *M.tb* pathogenesis, although challenges exist in isolating and modeling them. There is recent evidence that IMs from rhesus macaque lungs exhibit short lived and higher turnover rates compared to AMs. In contrast to AMs, ex-vivo stimulation of IMs with IFNγ and LPS significantly increased TNFα expression providing support for their role in regulating mucosal macrophage functions [93].

4. Macrophage PRRs

AMs express PRRs, which initiate signaling cascades in response to ligand recognition, and/or the engulfment and destruction of fluid and particulate matter via endocytosis. Involvement of specific receptors in the phagocytic process determines the cytoskeletal elements and signals involved in phagosome formation and maturation, resulting inflammatory response and, ultimately, intracellular fate of pathogen [94]. Several macrophage membrane and cytosolic PRRs are involved in recognition and response to *M.tb* that differ significantly depending on the macrophage source and experimental conditions.

4.1. Toll-like receptors

TLRs are generally considered to be pro-inflammatory, since their ligation leads to phosphorylation and deactivation of the NFκB -inhibitor, IκBα, resulting in NFκB activation and an inflammatory response. However, various TLRs also activate the signaling molecules TRIF and IRF, which result in increased IFN-β gene expression and an anti-inflammatory response [95]. Furthermore, recent evidence has reinforced the idea that TLRs can form complexes with other surface receptors to modulate the nature of the inflammatory response (reviewed in [96,97]). Relative to monocytes, human AMs express lower levels of TLR2, comparable levels of TLR4 and increased levels of TLR9 [98], and contrastingly, murine AMs do not express TLR9 [99] . The mycobacterial 19 kDa lipoprotein (LpqH)

interacts with TLR2 to induce TNFα, IL-12 and NO in both murine and human macrophages [100]. Other mycobacterial molecules, *e.g.*, LprA, LprG, PhoS1, LAM, LM and PIMs act as ligands for TLR2 leading to the production of IL-10, IL-4 and TGFβ [101] which can inhibit IFN-γ signaling in macrophages, allowing *M.tb* to evade host innate and adaptive immune responses. Other mycobacterial antigens, e.g. the 38kDa glycolipoprotein and PIM6 are sensed by TLR4/TLR2 and generate Th1-polarized cytokine responses in *M.tb*-infected mouse lungs [102,103]. Mycobacterial DNA generates a robust immune response through TLR9/TLR2 in murine macrophages [104]. Much work remains to be done in clarifying the role of TLRs in mycobacterial infection, particularly in regards to TLR cross-talk with non-TLR PRRs and phagocytic receptors in human cells.

4.2. Mannose receptor

The MR (CD206), a member of the C-type lectin family, is highly expressed on AMs [105,106], monocyte derived macrophages (MDMs) and DCs [107], but not on monocytes [108,109]. It interacts with endogenous mannose N-linked glycoproteins via its eight CRDs to maintain homeostasis [110] and also associates with mannose-containing surface PAMPs found on pathogenic microbes [reviewed in [111], representing a form of molecular mimicry for intracellular pathogens like *M.tb* [112]. It is the dominant C-type lectin on human AMs and monocyte-derived macrophages (MDMs) and, along with complement receptors, mediates the phagocytosis of *M.tb* [113]. This interaction shows specificity in that the MR can differentiate between *M.tb* strains [114] and binds to the mannose caps of mannosylated LAM (ManLAM) [115] and higher order PIMs (more mannosylated) found in greater amounts on pathogenic mycobacteria [25]. This receptor-specific interaction affects the fate of *M.tb* since entry through the MR leads to a decrease in phagosome lysosome (P-L) fusion [24,25] and an increase in the activity of Peroxisome Proliferator-Associated Receptor-γ (PPARγ, see below), leading to survival of intracellular bacteria [12]. The importance of the MR in mycobacterial infection is corroborated by evidence that MR polymorphisms are associated with enhanced susceptibility to *M. leprae* infection [116-120].

The MR is also a prototypic PRR linking innate and adaptive immunity [65,107,121-127]. These properties have been exploited to deliver DNA vaccines to APCs [126,128-130]. The MR may also contribute to the chronic stages of *M.tb* infection by mediating homotypic cellular adhesion and giant cell formation [131], which are characteristic in granulomas, and is a marker of AAMs [61,132]. The MR is being used in several ways to modulate the immune system for both therapeutic and vaccine purposes [130].

4.3. Scavenger receptors

Scavenger receptors comprise a large family (divided into 8 classes) that generally contribute to homeostatic functions of macrophages, being best characterized for their role in binding to oxidized low density lipoproteins (oxLDL) in the context of atherosclerosis [reviewed in [133]. However, scavenger receptor ligation leads to several downstream events, with outcomes ranging from the removal of unwanted self-molecules and apoptotic cells to the recognition of PAMPS in conjunction with TLR signaling [reviewed in [134]. Scavenger receptors play a role in *M.tb* binding to macrophages [135]. Three class A scavenger receptors are present on AMs: Scavenger Receptor A isoforms I and II (SRA-I/

II), and macrophage receptor with collagenous structure (MARCO). SR-A binds to most polyanionic molecules [136,137], and MARCO binds to and removes unopsonized environmental particles in the lung [138]. MARCO can tether mycobacterial trehalose-6,6-dimycolate (TDM) to the host cell surface, enabling pro-inflammatory signaling through TLR2 [139]. Knockout mice for SRA-I/II and MARCO are more susceptible to pulmonary pathogens and have a greater inflammatory response to inhaled particulate matter [140-142] indicating a host protective role for these receptors. Expression of the class B scavenger receptor CD36 is induced through PPARγ in human AMs [143] and contributes to the removal of apoptotic cells and oxLDL (reviewed in [144]). CD36 involvement in lipid removal contributes to foam cell generation during TB [145]. CD36 knockout mice fared better during early stages of *M.tb* infection [146] although the redundancy in scavenger receptor expression patterns complicates the interpretation of these results [147]. Much remains to be elucidated, but scavenger receptors' role in maintaining lung homeostasis places them in an important position during TB pathogenesis.

4.4. Mincle

Mincle (Clec4e), a C-type lectin family member, is highly expressed on mouse macrophages upon stimulation with LPS, TNFα, IL-6 and IFNγ [148]. Since Mincle does not contain an activating signal motif in the cytoplasmic region, it associates with the immunoreceptor tyrosine-based activation motif containing Fc receptor γ chain (FCRγ) to function as an activating receptor for damaged cells and fungi [149,150]. Mincle serves as a receptor for *M.tb* TDM to enhance inflammatory cytokine production leading to granuloma formation in mice [151,152].

4.5. Dectin I and II

Dectin I, a non-classical C-type lectin, is highly expressed in DCs, macrophages, monocytes and neutrophils [153]. There are 2 isoforms of Dectin I in mice and eight in humans, although only 2 have a CRD [154,155]. The Dectin I cytoplasmic region contains an ITAM motif for initiation of signaling cascades [156] by its ligands β-1,3 and β-1,6 linked glucans [157]. Dectin I activation by non-pathogenic mycobacteria *M. smegmatis* and *M. phlei*, and attenuated BCG and *M.tb* $H_{37}R_a$ strains enhances TNFα, IL-6 and RANTES in macrophages but fails to induce an inflammatory response to virulent *M.tb* $H_{37}R_v$ [158]. However, Dectin I and TLR4 mediate an IL-17A response by *M.tb* [159]. Consistent with earlier findings, we found that Dectin I activation by β-glucans inhibits the intracellular growth of *M. bovis* BCG but not virulent *M.tb* in human macrophages [160]. Inducible expression of Dectin I on non-phagocytic airway type II epithelial cells mediates antimicrobial effects against *M.tb* [161].

Expression of Dectin II, another C-type lectin [162] , is restricted to macrophages and DC subsets [163] and it associates with FcRγ for generating activation signals [164]. Dectin II can function as a receptor for *M.tb* ManLAM, inducing both a pro-and anti-inflammatory cytokine response and promoting T cell-mediated adaptive immunity in mice [165]

4.6. NOD proteins

NOD (nucleotide binding oligomerization domain-containing protein) like receptors (NLRs) are intracellular PRRs that recognize pathogens or PAMPs [166,167] and are expressed on

antigen presenting cells and epithelial cells. Both NOD1 and NOD2 detect bacterial peptidoglycan fragments such as d-glutamyl-meso-diaminopimelic acid (DAP) and muramyl dipeptide (MDP), respectively, to regulate innate immune responses [168]. *M.tb* produces a glycolated form of MDP (GMDP) that activates NOD2-dependent host immune responses in human and murine macrophages and mice [169,170]. *M.tb*-mediated immune responses are significantly reduced upon NOD2 knockdown in human macrophages and *M.tb* growth increased [171]. Consistent with this, NOD2 expressed in AMs recognizes MDP and induces IL-1β, IL-6 and TNF-α. Pretreatment of AMs with MDP significantly increased the intracellular killing of virulent *M.tb* by increasing expression of LL37 and autophagy proteins IRGM and LC3 [172].

5. Macrophage negative regulators of inflammation

Various regulatory molecules such as IRAK-M, the SOCS proteins and CD200R can suppress macrophage activation and thus are important in protecting the alveolar space from inflammatory damage[49,76,173]. There is some evidence for their role in TB pathogenesis [49,76,174-178].

5.1. IRAK-M

Interleukin-1 receptor associated M (IRAK-M) is an important negative regulator of innate immune responses [179-181]. Its expression is enhanced by TLR ligands indicating a negative feedback loop to dampen inflammation [180]. We have shown that basal expression of IRAK-M is higher in human AMs relative to MDMs and that MDM treatment with SP-A or Survanta (commercially available bovine surfactant) enhances IRAK-M expression, subsequently decreasing LPS-induced pro-inflammatory cytokine responses [49]. These data support the idea that AMs are immunologically shaped by the proteins and lipids in the lung alveolus. LAM-mediated up-regulation of IRAK-M dampens TLR4-mediated IL-12 p40 expression in murine macrophages [182] and *M.tb* infection delays the Th1 immune response by up-regulating the expression of IRAK-M expression in lung APCs in mice [183].

5.2. SOCS proteins

Expression of the 8 suppressor of cytokine signaling (SOCS) family of proteins is induced in macrophages following cytokine stimulation, which blocks further inflammatory signaling in a classic feedback loop [184,185]. Several microorganisms, including *M.tb*, have developed sophisticated strategies to hijack SOCS protein pathways in order to block immune defense signaling pathways [174]. *M. avium* infection enhances SOCS1 and SOCS3, which correlates with a lack of IFNγ-mediated signaling in human macrophages [175]. Similarly, *M.tb* infection enhances SOCS expression in murine and human macrophages and the subsequently impaired IFNγ secretion results in enhanced bacterial load [176,186]. SOCS1 knockdown in murine macrophages significantly enhances the ability of infected macrophages to clear *M.tb* through an IFNγ–dependent mechanism [176,178]. Finally, SOCS1 mRNA transcripts are increased in the peripheral blood mononuclear cells (PBMCs) of advanced pulmonary TB patients when compared to moderately infected patients [187,188].

5.3. CD200R

CD200R is an immunoglobulin superfamily member expressed on most leukocytes, particularly cells of the myeloid lineage [7,189-191] and Th2 polarized T cells [189]. Engagement of CD200R by its only known ligand, CD200, inhibits the activation of both myeloid and T cells. CD200R is expressed on murine AMs and plays a critical role in mediating homeostasis in the lung environment [76]. CD200 is highly expressed on type II alveolar epithelial cells and apoptotic leukocytes in the inflamed airway [76,173]. CD200 knockdown results in an increase in AM number and spontaneous up-regulation of activity [76]. CD200 knockout mice succumb to a sub-lethal dose of influenza virus due to uncontrolled inflammation [76]. These data illustrate the critical role of CD200R in the chronic suppression of AM activation, a topic of current interest in our laboratory.

6. Macrophage immunoregulatory cytokines

Cytokines fall in 3 general classes: innate, adaptive, and stimulators of hematopoiesis. Studies of the host cytokine responses TB infection are abundant and vary markedly depending on the model and mammalian species used. It has become clear that *M.tb* generates cytokine responses in all 3 categories and that the “optimal” protective response to infection will represent a balance of the various cytokines produced. In addition, most of these cytokines have pleiotropic effects depending on the context of their activation and local tissue environment. Thus, it is difficult to correlate host protection with any particular cytokine. Here we will focus on two important immunoregulatory macrophage cytokines for *M.tb*: IL-10 and type I IFNs.

6.1. Interleukin 10

IL-10 is produced by many cell types and was initially shown to inhibit synthesis of IFNγ in Th1 cells [192-194]. Human IL-10 shares 80% homology with murine IL-10 [195]. Binding of IL-10 to its receptors, IL-10 R1 and IL10R2, results in activation of Jak1 and Tyk2, which subsequently activate STAT-1, 3 and 5 [195]. IL-10 can suppress Ag presentation as well as production of pro-inflammatory cytokines, chemokines, adhesion molecules and co stimulatory molecules in macrophages and other cell types [196]. IL-10 also inhibits nuclear translocation of NFκB and blocks DNA binding activity of translocated NFκB [197]. IFNγ-inducible genes are suppressed by IL-10 through inhibition of STAT1- and 3-mediated induction of SOCS3 [196,198-200]. Pulmonary TB patients have increased levels of IL-10 and TGFβ in their bronchoalveolar lavage (BAL) fluid [201,202] and serum [203]. Both IL-10 and TGFβ can inhibit CD4 T cell proliferation and IFNγ production in PBMCs from healthy PPD^+ patients, possibly through the inhibition of APC function [204,204,205]. Additionally, neutralization of IL-10 produced by PBMCs from active TB patients results in increased T cell proliferation and enhanced IFNγ production [204,206]; the same trend was observed in patients with anergic TB [207]. Increased sputum IL-10 levels of active TB patients correlate with increased levels of *M.tb* antigen CFP32 [208]. Also IL-10 production following *M.tb* infection of human MDMs or AMs blocks phagosome maturation [209]. Finally, IL-10 polymorphisms are associated with susceptibility to TB [210-212]. Collectively, these human studies provide strong evidence that IL-10 acts a limiting factor for optimal host immune responses to *M.tb*.

Results on IL-10 in *M.tb* pathogenesis in mice are variable, partly dependent on the mouse strain used. Early studies in the IL 10 $^{-/-}$ mouse (C57Bl/6 background) showed that despite increased IFNγ levels during every stage of infection, IL-10 deficiency did not result in a significant difference in lung bacterial load compared to wild type mice following aerosol infection [213-215]. In contrast, others have reported that IL-10 deficient mice (C57BL/6, CBA/J and BALB/c) show increased resistance to aerosol *M.tb* infection, with reduced lung bacterial load and increased IFNγ [216-218]. IL-10 over-expression in mice did not increase the susceptibility of mice during early stages of *M.tb* infection, but there was increased reactivation and higher lung bacterial burdens during the chronic phase of infection [219]. Another study demonstrated that *M.tb* infection of IL10 $^{-/-}$ mice treated with anti-IL-10R monoclonal antibody have reduced lung and spleen bacterial growth when compared to control mice [217]. Macrophages infected with *M.tb* or BCG have reduced surface expression of IFNγ-mediated MHC class II molecules due to IL-10-dependent inhibition [220]. Finally, blockade of IL-10 signaling during BCG vaccination increases the efficacy of the vaccine against *M.tb* [221]. On balance, mouse studies are generally congruent with human studies with regard to the immunoregulatory effects of IL-10.

6.2. Type I interferons

Type 1 Interferons (IFNs) are produced in response to many pathogens and can subvert anti-TB host defenses by inhibiting production of iNOS, IL-12 p40, IL1-α and IL-1β, while inducing mediators of immune suppression such as IL-10 and IL1R antagonist [222,223]. Although type I and type II IFNs share similar STAT1-dependent signaling pathways, type I IFNs appear to promote bacterial growth. *M.tb* and activation of TLR2 significantly reduce the expression of TLR9-mediated type I IFNα/β and DC Ag presentation [224]. Type I IFNs are increased during *M.tb* infection and *M.tb*-infected type I IFN receptor deficient mice display lower bacterial burden when compared with wild type mice [225,226]. Intranasal delivery of a type I IFN inducer to *M.tb*-infected mice results in exacerbated lung pathology and increased bacterial load in the lungs [227]. The *M.tb* ESX-1-mediated secretion system can mediate the Type I IFN response during infection [228,229]. The relevance of these findings to human TB is supported by evidence that type I and II IFN-induced genes dominate the whole blood transcriptional profile of TB patients and this gene signature correlates highly with disease severity [230]. In human leprosy the expression of host protective IFN-γ and host susceptible IFN-β is inversely correlated [231]. The IFN-γ induced vitamin D-dependent macrophage antimicrobial peptide response was significantly inhibited by IFN-β and downstream IL-10 during *M. leprae* infection [231]. Recent studies demonstrate that IL-1 confers host resistance through the induction of eicosanoids that limit excessive type I IFN production and foster bacterial containment [232]. Further, the study showed that reduced IL-1 response and excessive type I IFN induction in infected mice and humans are linked to an eicosanoid imbalance associated with disease exacerbation [232].

7. Macrophage immunoregulatory transcription factors

7.1. Peroxisome Proliferator-Associated Receptor-γ

The nuclear receptor-associated transcription factor PPARγ acts as a negative regulator of macrophage activation by trans-repression of the transcription factors NF-κB, AP-1 and

STAT [233-235] and attenuating the respiratory burst [234,236,237]. PPARγ expression is high in AMs and its deletion in AMs increases Th1-associated gene expression such as iNOS, IFN-γ, IL-12 p40, MIP1α and IP-10 [238]. These attributes have important implications for controlling *M.tb* infection. Mycobacterial infection causes increased PPARγ expression in human and murine macrophages through PRRs such as the MR and TLRs [12,239], while PPARγ knockdown in infected human macrophages increases anti-mycobactericidal activity and TNFα production [12,145]. *M.tb*-mediated induction of PPARγ also regulates host cell metabolism, leading to increased lipid body formation and down-regulation of the host immune response [239].

7.2. Liver X receptor

The liver X receptors (LXRs) are a second class of nuclear receptors activated by oxidized lipids. LXRs are mainly considered cholesterol sensors that regulate the expression of genes in lipid metabolism in response to specific oxysterol ligands [240,241]. In macrophages, these ligands may be derived from internalized oxLDL or generated intracellularly through cholesterol modification. Macrophage lipid import and export mechanisms are tightly regulated, since unbalanced lipid homeostasis affects the inflammatory status of the organism. Recently, LXRα and LXRβ have emerged as master regulators of macrophage transcriptional programs involved in cholesterol, fatty acid and glucose homeostasis [242-244] [241,245], and also negatively regulate macrophage inflammatory gene expression such as iNOS, COX2 and IL-6 [241]. Persisting *M.tb* in lung granulomas use lipids as the sole carbon source for growth [246] and mycobacterial persistence is critically linked to its ability to acquire and catabolize cholesterol from the host [247]. In addition, cholesterol is essential for *M.tb* phagocytosis by macrophages and for inhibition of phagosome maturation [248]. Intratracheal infection of mice with *M.tb* enhances LXR and LXR-dependent gene expression [249]. Further, mice deficient in both LXR isoforms were susceptible to *M.tb* infection, developing higher bacterial burdens and increased granulomatous lesions [249]. LXR knockout mice exhibit dysregulation of both pro- and anti-inflammatory functions [249]. An LXR gene polymorphism is associated with *M.tb* susceptibility [250] further emphasizing the importance of LXRs in the protective immune response against *M.tb*.

7.3. TR4

Testicular orphan receptor 4 (TR4) (aka TAK1 and Nrc2c2) does not have an identified ligand but is expressed in numerous tissues, including in macrophages [251,252].Upon activation, TR4 can repress genes targeted by PPARγ, LXR, vitamin D3 receptor and thyroid hormone receptor [252]. TR4 deficiency decreases CD36 expression and reduces foam cell formation in mice [253]. TR4-mediated CD36 transactivation is enhanced by polyunsaturated fatty acids and their metabolites, as well as the synthetic PPAR agonists [253]. TR4 knockdown in human macrophages enhances their ability to control *M.tb* growth by lowering CD36 expression and decreasing foam cell formation [145]. The same group reported that *M.tb* oxygenated keto-mycolic acids function as ligands for TR4 and increase its transcriptional activity, resulting in increased abundance of foam cells and granuloma formation [254]. Thus, PPARγ and TR4 appear to synergistically contribute to *M.tb*-induced

lipid biogenesis through increased CD36 expression and modulate foam cell formation by driving macrophages towards an immunosuppressive phenotype.

8. Macrophage lipid metabolism

Host-derived lipid mediators play an important role during *M.tb* infection and glycolipids from the mycobacterial cell wall can also function as potent antigens and immunomodulators [255,256]. Mycobacterial metabolism of host lipids serves as a source of nutrients [247] and protection from oxidative damage during infection [257], while dysregulation of host lipid metabolism contributes to foamy macrophage generation and granuloma caseation, leading to bacterial persistence [246]. This section will focus on macrophage prostaglandins, lipoxins and leukotrienes during *M.tb* infection. These polyunsaturated eicosanoids (20-carbon fatty acids) are hydroxylated during enzymatic modification of essential fatty acids and contribute to both homeostasis of the immune system and disease processes (reviewed in [258]).

8.1. Prostaglandins

Prostaglandins (PGs) are derived from the membrane fatty acid arachidonate and are produced by virtually all cells [259,260]. PGs can induce chemokines to enhance trafficking of myeloid cells to inflamed tissues [261] and contribute to the amplification of pro-inflammatory cytokine production [262]. The type of PG produced is tissue specific; however, the bulk of these molecules are deactivated in the lungs after entering the circulatory system [258]. PGJ_2, in opposition to the majority of PGs, has predominantly anti-inflammatory effects and acts as an endogenous ligand for PPARγ [263]. As mentioned earlier, PPARγ activity can increase intracellular survival of virulent *M.tb* in macrophages with a decrease in TNFα production [12]. Through PPARγ activation, PGJ_2 production may thus be detrimental to the host during *M.tb* infection.

PGE_2 expression in mice gradually increases during *M.tb* infection [264]. Low levels of PGE_2 during early infection were necessary to control the infection, due to PGE_2-dependent iNOS production [264] and stabilization of the T cell response [265]. However, during later chronic infection, lipid-laden infected macrophages express high PGE_2 levels, which can inhibit the inflammatory response and contribute to progressive pneumonia [264]. Thus, the concentration and kinetics of PG expression are important in considering their role during TB pathogenesis.

8.2. Lipoxins

Lipoxins (LXs) are produced by leukocytes [266], pulmonary endothelial cells and macrophages during *M.tb* infection [267]. LXs are known as pro-resolving lipid mediators, a class which also includes resolvins and protectins [266], contributing to the cessation of the inflammatory response [268]. They have autocrine and paracrine effects [268]. To mediate resolution of inflammation, LXs function to inhibit neutrophil migration and degranulation [269], and prevent pre-mature macrophage apoptosis. The 5- and 15-lipoxygenases (LOs) use arachidonic acid as a substrate for the production of 15-epilipoxin-A_4 and leukotriene B_4 (see below). 15-epi-LXA_4 can inhibit the production of IL-6, TNF-α and IL-8 [270,271].

Mice lacking 5LO, the enzyme responsible for LXA_4, are more resistant to *M.tb* infection than wild type controls, attributed to increased production of IL-12, IFNγ and iNOS. Knockout mice given an LXA_4 analog reverted to the wild type infection response [267]. Infection of human and murine monocytes with *M.tb* increases LXA_4 production, which blocks PGE_2-dependent repair of the cell membrane, causing necrosis and dissemination of bacteria [272]. As with PGJ_2 and PPARγ, the anti-inflammatory functions of LXA_4 appear to work against the host in this disease.

8.3. Leukotrienes

Lipoxygenase enzymes are responsible for the production of leukotrienes (LTs) through the conversion of arachidonate to hydroxyeicosatetraenoic acid (HETE). 5-HETE is further converted to the unstable LTA_4, the precursor to all other LTs [273]. The main sources of LTs are macrophages, neutrophils, DCs and mast cells. LTs are pro-inflammatory molecules that induce smooth muscle contraction and vasoconstriction, contributing to allergies [274,275], asthma [276] and autoimmune diseases [277].

LTs are host protective in the mouse. *M.tb*-infected BALB/c mice given the drug celecoxib (LTB_4 stimulator/PGE_2 inhibitor) exhibited a slight increase in survival. Conversely, the LTB_4 synthesis inhibitor MK886 reduced 60 day survival rates by half [278]. LTB_4 is also important for human neutrophil killing during BCG infection [279]. However, BALB/c mice treated with MK866 are still protected from TB when pre-treated with a prime-boost heterologous vaccine [280], indicating that the effects of LTs can be overridden. LTB4 is induced in both human TB and the zebrafish model of *M.tb* infection [281,282], and its levels regulate host protection [283].

9. Macrophage microRNAs

9.1. miRNA function and biogenesis

MicroRNAs (miRNAs) are endogenous, non-coding, small RNAs that function as gene regulators by primarily mediating translational repression or degradation of target mRNAs [284]. They are implicated in a variety of biological processes [285] and are transcribed from intergenic or intragenic regions of the genome in pri-miRNA form, which may contain one or multiple miRNAs. [286]. Although the role of miRNAs in regulation of the immune system and response to infection is becoming clearer, we do not yet have a clear picture of the global impact of miRNAs on the immune response to *M.tb*. Recent evidence indicates that there is one and that macrophage immune pathways play a role.

9.2. miRNAs in *M.tb* infection

Several studies have compared miRNA profiles in TB patients (active or latent) verses healthy controls, with little agreement between the reports. These profiles were obtained from serum and sputum, which mostly rely on detection of extracellular sources of miRNAs; thus, miRNA profiles obtained in this fashion may not be truly indicative of *M.tb*-induced processes [287-291].

There are recent studies of miRNAs in *M.tb* infection with validated targets. However, some were carried out exclusively in murine models or murine cell lines and although miRNAs are conserved between species, regulation of their expression may differ, and so miRNA expression patterns and their targets must be validated in human model systems [292-294]. It was reported early that there is increased expression of miR-144* in the PBMCs of pulmonary TB patients. This increase was later localized to the T cell population and observed to inhibit IFN-γ and TNF-α secretion[295]. Soon after, we reported increased miR-125b expression with virulent *M.tb* infection (but not with avirulent *M. smegmatis*) which resulted in destabilization of TNF-α mRNA and decreased TNF-α secretion in human primary macrophages [255]. These studies indicate that modulation of cytokine production by miRNAs may be an effective mechanism for *M.tb* to escape immune control.

M.tb may also inhibit apoptosis through miRNAs. miR-29a targets the anti-apoptotic proteins B-cell lymphoma 2 (Bcl-2), myeloid cell leukemia -1 (Mcl-1) p85a and GTP-binding protein CDC42 [296] and *M.tb* infection can suppress miR29a [297], thereby potentially inhibiting apoptosis. Additionally, miR-29a targets the 3'UTR region of IFN-γ mRNA, suppressing IFN-γ production. miRNA-29a expression was down-regulated after BCG infection and miR-29a knockdown induced IFN-γ expression in NK cells and T cells, and promoted murine survival after *M.tb* infection [297].

Mycobacteria can modulate TLR signaling pathways through up-regulation of various miRNAs. In murine AMs and cell lines, high levels of miR-124 were detected in response to BCG infection. miR-124 inhibits TLR signaling by down-regulating the expression of MyD88, TRAF6 and TLR6 [298]. Patients with active TB have increased levels of miR-147 [299], which acts as a negative regulator of TLR/NFκB-mediated pro-inflammatory cytokines such as TNF-α and IL-6 [300]. However, TNFα and IL-6 levels in sputum did not differ significantly between active TB and control groups. The anti-inflammatory miRNA, miR-99b, was highly up-regulated in *M.tb*-infected DCs and macrophages and blockade of miR-99b expression significantly reduced bacterial growth in DCs and increased TNFα, IL-6, IL-12 and IL-1β [294]. Autophagy pathways are also influenced by miRNAs. miR-155 expression was enhanced in murine macrophages upon *M.tb* infection, leading to increased autophagy-mediated killing [301]. miR-155 targets the 3'-UTR region of Ras homologue enriched in brain (Rheb), a negative regulator of autophagy. Finally, a host-protective increase in miR-223 expression was observed during miRNA expression profiling of TB patient blood and lung tissue, followed by functional studies in a miR-223 knockout mouse [302]. These studies indicated that miR-223 directly targets CXCL2 and CCL3, and IL-6 to regulate neutrophil chemotaxis and inflammatory function.

miRNAs potentially serve as a biomarker for TB disease diagnosis and prognosis. However, importantly, individual miRNAs or miRNA families can regulate hundreds of genes and, conversely, gene targets can be regulated by different miRNAs. Thus, a clear picture of miRNAs and other non-coding RNAs in TB pathogenesis will require further study.

10. Differences in macrophage biology between man and mouse

Although murine models have been used extensively to study TB pathogenesis, or identify and test drug and vaccine candidates for subsequent human trials, there is more evidence and attention to the substantial differences between the two species in the nature of their inflammatory pathways, in ways that impact our understanding of TB pathogenesis [303]. For example, in terms of fundamental aspects of host defense, macrophages from humans and mice differ in expression/activity of PRRs, including TLRs and C-type lectins [304-306], signaling pathways [307,308], autophagy pathways [305], and host defense molecules such as antimicrobial peptides [309] and NO [310,311] to name a few. Mouse KO studies targeting host defense pathways have often yielded negative findings leading to interpretations contrary to in vitro findings despite these known differences between species as well as the known redundancy in the innate immune system, a cardinal feature of this evolutionarily conserved arm of immunity. Thus, future studies must take these differences into account and continue to foster new animal models that better reflect human in vitro and in vivo systems to advance the field.

11. Conclusions

Recent focus on the plasticity and functional diversity of macrophages has raised new and important questions for the TB community in terms of assessing: 1) organ-specific effects, particularly in regards to the lung; 2) macrophage activation states; 3) differences in macrophage function and protective responses during the continuum of TB (primary infection, latency and re-activation); 4) in vitro cultivation conditions [e.g. recent studies on TB and diabetes highlight the importance of using autologous serum with macrophages to maintain undefined soluble immune factors [312], and 5) similarities and differences among mammalian macrophage sources. As we gain more knowledge about macrophage responses in the context of organ-specific microenvironments, our understanding of the molecular details underlying the pivotal *M.tb*-macrophage interactions occurring during TB will become more defined.

Abbreviations

IM	Interstitial Macrophage
DPPC	Dipalmitoylphosphatidylcholine
CRD	Carbohydrate recognition domain
CAM	Classically activated macrophage
AAM	Alternatively activated macrophage
SP	surfactant protein
ManLAM	mannosylated lipoarabinomannan
PIM	phosphatidyl inositol mannoside
LM	lipomannan

P-L fusion	phagosome-lysosome fusion
AM	alveolar macrophage
DPPC	dipalmitoyl phosphatidylcholine
BAL	bronchoalveolar lavage
M.tb	*Mycobacterium tuberculosis*
PG	prostaglandin
LX	lipoxin
LT	leukotriene
miRNA	microRNA

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Highlights

- We review current concepts in macrophage responses to *M. tuberculosis*
- We emphasize macrophage heterogeneity and the unique immunoregulatory alveolar macrophage
- We describe major macrophage immunoregulatory pathways that influence the host inflammatory response to *M. tuberculosis*
- We compare similarities and differences in macrophage responses among different sources

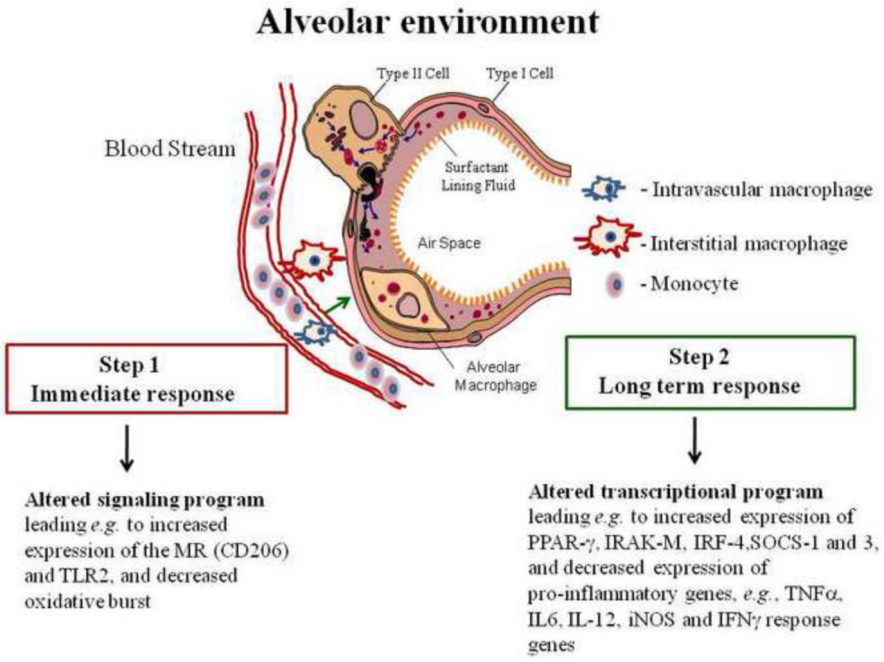

Figure 1. Depiction of the generation of AMs within the alveolar tissue environment

Blood monocytes traverse the pulmonary alveolar capillary bed and differentiate into intravascular macrophages in situ or transit to the interstitium to become interstitial macrophages (IMs), or to the alveolar space to become AMs (there is also evidence for local production of macrophages in mice). On route, the macrophages are “shaped” by locally produced determinants such as cytokines like GM-CSF, etc. Upon entering the alveolar space, AMs encounter surfactant components which play a role in differentiating these cells to their unique immunoregulatory phenotype, enabling them to acquire their primary function of enhancing clearance of particulates while limiting excessive pro-inflammatory “collateral” damage. Step 1 AM changes are immediate as a result of surfactant components, and other ligands, engaging their cognate receptors to generate a signaling cascade which alters the phenotype and function. Step 2 is long term resulting from an alteration in transcriptional programming. The unique AM phenotype requires constant input from the alveolar environment.

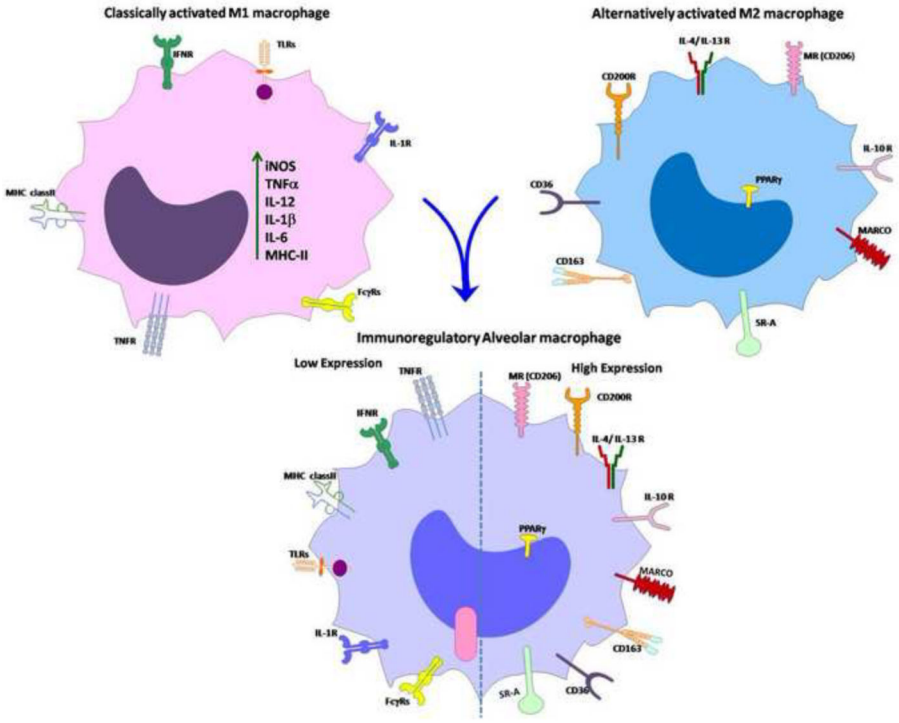

Figure 2. Schematic of macrophage activation by different stimuli that drive macrophage differentiation to different phenotypes

(a) Classically activated M1 macrophages are differentiated by IFN-γ, LPS and TNFα which lead to increased expression of pro-inflammatory mediators such as cytokines (TNFα, IL-1β, IL-12 and IL-6), iNOS, MHC-II molecule, and TLRs, as well as increased expression of FcγRs. (b) Alternatively activated M2 macrophages are differentiated by IL-4 and IL-13 which lead to an anti-inflammatory signature with increased expression of the MR (CD206), PPARγ, IL-10, CD200R, CD163, CD36, MARCO and SR-A. (c) AMs are unique immunoregulatory cells which express both M1 and M2 markers. Their activation is tightly regulated by molecules such as PPARγ, IRAK-M, IL-10 and SOCS proteins.

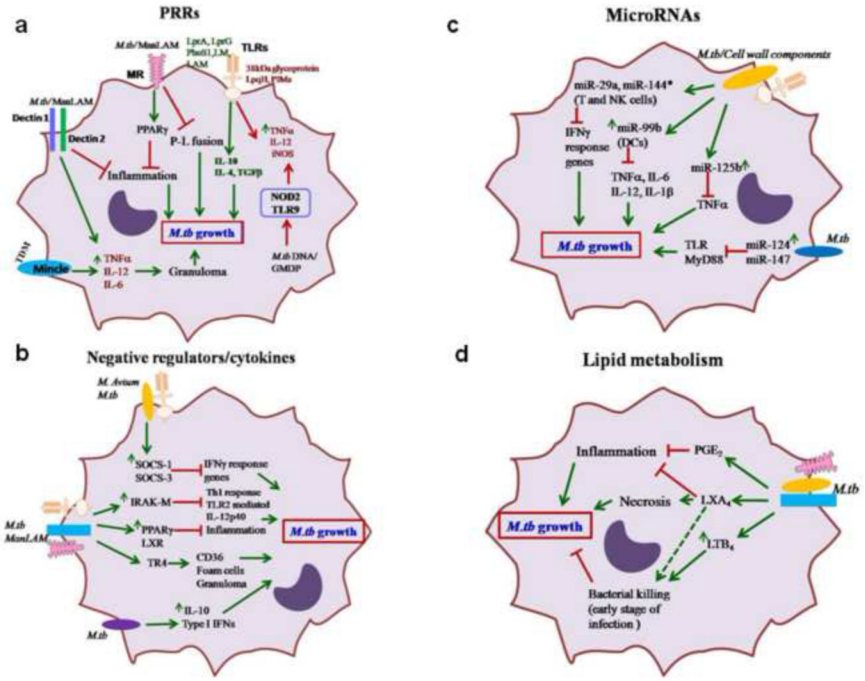

Figure 3. Schematic of macrophage regulatory factors that alter *M.tb* growth

(a) Activation of PRRs by *M.tb* and/or *M.tb* cell wall components, and downstream responses. TLR activation by *M.tb* cell wall components 38 kDa glycoprotein, LpqH, or PIMs promote inflammation; in contrast, LprA, LprG, PhoS1, LM and LAM increase the expression of anti-inflammatory mediators such as IL-10, IL-4 and TGF-β which enhance *M.tb* growth. MR-mediated phagocytosis of *M.tb* or MR stimulation by ManLAM delays P-L fusion and enhances PPARγ expression, leading to increased *M.tb* growth. TDM binding to Mincle or ManLAM to Dectin II enhance TNF1, IL-12 and IL-6 leading to granuloma formation and *M.tb* control. (b) Negative regulators of macrophage responses to *M.tb* and/or cell wall components. *M.tb* or ManLAM stimulation enhances the expression of various negative regulators, *e.g.* IRAK-M, SOCS-1 and SOCS-3, PPARγ, and TR4 as well as IL-10 and type I-IFNs which suppress host protective inflammatory mediators and promote *M.tb* growth. (c) Regulation of macrophage microRNAs and their functions in response to *M.tb* and/or cell wall components. miRNAs are important immune regulators during *M.tb* infection. Increased miR-125b targets TNFα for degradation, and miR-124 and miR-147 target TLR pathway genes such as MyD88 and TRAF6, are highly induced by *M.tb* infection and promote *M.tb* growth. (d) Impact of macrophage lipid mediators in response to *M.tb* and/or cell wall components. Lipid metabolites such as PGE_2, LXA_4 and LTB_4 also regulate the macrophage immune response during *M.tb* infection. PGE_2 and LXA_4 are anti-inflammatory and promote *M.tb* growth. In contrast, LTB_4 enhances bacterial killing during the early stage of infection and later promotes *M.tb* growth.