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Macrophages in Tuberculosis: Friend or Foe

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Abstract

Tuberculosis (TB) remains one of the greatest threats to human health. The causative bacterium, *Mycobacterium tuberculosis* (Mtb) is acquired by the respiratory route. It is exquisitely human-adapted and a prototypic intracellular pathogen of macrophages, with alveolar macrophages (AMs) being the primary conduit of infection and disease. The outcome of primary infection is most often a latently infected healthy human host, in whom the bacteria are held in check by the host immune response. Such individuals can develop active TB later in life with impairment in the immune system. In contrast, in a minority of infected individuals, the host immune response fails to control the growth of bacilli, and progressive granulomatous disease develops, facilitating spread of the bacilli via infectious aerosols coughed out into the environment and inhaled by new hosts. The molecular details of the Mtb-macrophage interaction continue to be elucidated. However, it is clear that a number of complex processes are involved at the different stages of infection that may benefit either the bacterium or the host. Macrophages demonstrate tremendous phenotypic heterogeneity and functional plasticity which, depending on the site and stage of infection, facilitate the diverse outcomes. Moreover, host responses vary depending on the specific characteristics of the infecting Mtb strain. In this chapter, we describe a contemporary view of the behavior of AMs and their interaction with various Mtb strains in generating unique immunologic lung specific responses.

Keywords

Alveolar macrophage; tissue microenvironment; *Mycobacterium tuberculosis*; granuloma

1. Tuberculosis

1.1 Human infection: Latency and disease

Mycobacterium tuberculosis (Mtb) is an exquisitely adapted human pathogen that infects an estimated 2 billion people [1]. Infection occurs following inhalation of aerosolized droplets containing viable bacilli. Once inhaled, the bacilli are phagocytosed in the air spaces primarily by resident alveolar macrophages (AMs) and dendritic cells (DCs). Following lung exposure, Mtb-infected phagocytes can migrate from the alveolar space into the lung

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interstitium and then, via the lymphatic and hematogenous routes, disseminate to other organs [2]. Subsequently, the bacilli may grow unimpeded within host macrophages, resulting in primary progressive disease or reactivation disease after a short period of latency, as seen in about 10% of immune competent individuals. Alternatively, bacillary growth may be controlled, and the bacteria may be killed or may adapt to survival within cellular granulomas in a non-replicating state, thereby establishing a latent infection, as is seen in approximately 90% of otherwise healthy hosts. Latent infection can persist for decades after exposure to Mtb before reactivating to cause active disease (primarily in the lungs), when the immune-mediated control of bacillary growth fails, as seen for example following human immunodeficiency virus (HIV) infection [3]. The ability of Mtb to establish latency, combined with the massive exposure of individuals to infectious organisms in hyperendemic areas of the world, is responsible for the huge reservoir of latently infected individuals. The Global Burden of Disease Study determined that, globally, tuberculosis (TB) is the 7th leading cause of Disability Adjusted Life Years (DALYs) and, unlike most infectious diseases, will still be among the top ten causes of DALYs in 2020 [4]. Thus, an understanding of mechanisms through which Mtb bacilli interact with host macrophages (particularly AMs), grow, persist and reactivate, is crucial to the development of new tools for improving TB control.

2. The macrophage

2.1 Macrophage heterogeneity and plasticity

Macrophages serve as the major host cell niche for the growth and survival of Mtb. However, these cells are also responsible for activation of the protective immune responses, both innate and acquired, which are necessary to control or eliminate the infection. Macrophages, derived from hematopoietic cells in the bone marrow [5,6], differentiate from promonocytic cells to mature monocytes in the peripheral blood and further into macrophages, following migration into tissue where they maintain homeostasis (low-level recruitment) or are recruited in response to inflammation/infection (high-level recruitment) [7,8]. Macrophages are present in almost all tissues throughout the body. Their pattern of differentiation is highly dependent on the local environment, including the tissue location and associated cells, as well as growth factors and cytokines present at each site. Through the expression of various cell surface receptors, the macrophage recognizes, binds and internalizes foreign particles, including Mtb. This initiates a complex process of control of intracellular growth of the bacilli via a cascade of signaling events that result in the release of soluble and cell-associated antimicrobial and innate immune mediators [9].

Early macrophage biology studies revealed heterogeneity, functional and morphologic, often based on phenotyping the diverse cell populations using antibodies [10–13]. More recent advances in genetics, isolation of monocyte subsets, improved DNA microarrays and proteomics have allowed scientists to reconsider macrophage activation phenotypes in more detail [14–22]. The heterogeneity observed reflects the plasticity and adaptation of the cells to different anatomical and immunologic locations. For example, high expression of a subset of pattern recognition receptors (PRRs) on AMs appears to be associated with the ability of these cells to clear particles and microbes from the lungs without causing excessive inflammation (see below). Recent studies have suggested that the initial interaction of macrophages with soluble mediators, such as cytokines, determines the functional phenotype of the cells; others have shown that macrophages can be continuously altered as the environment changes [23–28]. These observations help explain the fact that Mtb interactions with macrophages can vary greatly depending upon the local microenvironment in which they occur.

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For simplicity, macrophage heterogeneity has been categorized into four major groups defined primarily by *in vitro* cell culture under different conditions: type I and type II macrophages, alternatively activated macrophages and deactivated macrophages [15,29–32]. Type I macrophages (classical activation or M1 cells) are differentiated by *in vitro* culture with the lymphoid cell mediator interferon gamma (IFN-γ) and lipopolysaccharide (LPS), a Gram-negative microbial trigger which induces pro-inflammatory cytokine production. Type II macrophages (innate activation) are differentiated in *in vitro* culture by ligation of receptors by immune complexes. Both of these macrophage phenotypes are associated with high microbicidal activity, the production of pro-inflammatory cytokines [tumor necrosis factor alpha (TNF-α), interleukin 1 beta (IL-1β) and interleukin 6 (IL-6)] and reactive oxygen species (ROS), and the activation of inducible nitric oxide synthase (iNOS), the latter leading to the synthesis of nitric oxide (NO) [33]. Type I macrophages also have increased major histocompatibility complex (MHC) class II and cluster of differentiation (CD) 86 (CD86) expression, and increased antigen presentation. Differences between them include decreased mannose receptor (MR, CD206) expression in type I macrophages, while type II macrophages have increased production of the immunoregulatory cytokine interleukin 10 (IL-10) and decreased production of the pro-inflammatory cytokine interleukin 12 (IL-12) [30,31]. Thus, the two macrophage populations, although phenotypically similar, have distinct functional profiles.

The third major group is the alternatively activated macrophage (or M2 cells) [30,34,35]. These cells result from *in vitro* culture with the T_H2-type cytokines, interleukin 4 (IL-4) or interleukin 13 (IL-13), which decrease cellular responsiveness to IFN-γ and inhibit the synthesis of iNOS [30]. Glucocorticoids are also able to induce an alternative macrophage activation state [32]. Alternatively activated macrophages have increased PRR expression, particularly of the MR, with decreased CD14 expression. Additionally, these cells do not produce large amounts of oxidants or pro-inflammatory cytokines, but rather secrete some anti-inflammatory cytokines (e.g. transforming growth factor beta (TGF-β)) [30,31] and decrease the T_H2 response likely by regulating the stimulation of lymphocytes [36]. This macrophage population has been associated with tissue repair and humoral immunity. Finally, the deactivated macrophage phenotype is induced by *in vitro* culture in the presence of cytokines such as IL-10 or TGF-β, or by ligation of inhibitory receptors (*i.e.*, CD200-CD200R, CD47- CD172a or esteroids). This macrophage phenotype has been associated with anti-inflammatory cytokine production, prostaglandin E_2 (PGE_2) production and reduced MHC II expression [30].

Although this classification provides a useful framework for studying and understanding macrophage heterogeneity, it is undoubtedly simplistic and lacks the impact of specialized local *in vivo* microenvironments on the macrophage phenotype [37–41]. A more flexible classification has been suggested recently where macrophage heterogeneity, generated in response to innate or acquired immune responses, is considered to be a spectrum, wherein different cell populations, such as classically activated macrophages, wound healing macrophages and regulatory macrophages, may overlap in their functions, representing different points along a spectrum [42].

2.2 Macrophages in the Mtb granuloma

Phagocytosis of Mtb by AMs and DCs initiates a cascade of events involving the production of cytokines and chemokines, which stimulate the activation of phagocyte anti-microbial activities and recruit blood polymorphonuclear leukocytes (PMN) and additional mononuclear leukocytes into the tissue to the site of infection. The accumulation of mononuclear leukocytes around foci of infected cells leads to the formation of a macrophage-rich cell mass known as the granuloma. Macrophages play an essential role in the formation of Mtb granulomas. The macrophage population within these structures has a

high turn-over rate and is diverse, including epithelioid cell, multinucleated giant cell (MNG) [43] and foamy cell [44] phenotypes. The role of the granuloma is to control the growth of intracellular Mtb and to limit bacillary dissemination. Persistence of the granuloma depends on local production of T_H1 type cytokines by antigen-specific T lymphocytes, responding to the presence of Mtb antigens and leading to sustained phagocyte activation, inflammation and anti-microbial activity. If optimal, the anti-microbial granulomatous response to infection leads to complete bacillary control and latency. As the bacilli are controlled and latent infection is established, the granulomas decrease in size and cellularity, and the lungs typically show no clinical signs of disease by chest X-ray [45]. However, when the granulomatous response is not fully protective, the bacilli continue to replicate and active TB disease ensues. The lungs of such individuals contain enlarging granulomas that differentiate with time, leading to the development of cavitary pulmonary disease. A complex set of interactions between host macrophages and their response to the infecting bacilli, as well as the specific properties of the Mtb strain, are presumed to be responsible for determining the outcome during this process.

Histopathologic examination of lesions in the lungs of humans with advanced pulmonary disease reveals heterogeneous cellular architecture, most prominent in the concentrically layered cavitating and non-cavitating necrotic granulomas seen in patients with sputum-positive TB. Cross-sections of large cavitating lesions show loose cellular accumulation at the luminal surface of the cavity, consisting of numerous PMNs and macrophages, surrounded by a layer of acellular caseous necrotic material. In non-cavitating closed granulomas, the central necrotic area is fully acellular. Subtending the acellular necrotic layer in both types of lesions, there is granulomatous-fibrotic tissue with a mixed mononuclear leukocyte infiltrate consisting of Langerhans-type giant cells, epithelioid macrophages, foam cells and many scattered lymphocytes [46]. Acid-fast bacilli (AFB), apparently cell-associated, can be detected in large numbers at the cavity surface; while the granulomatous-fibrotic layer, with abundant macrophages, MNGs, and lymphocytes, is essentially devoid of visible AFB. In addition, AFBs are seldom seen in AMs residing within airspaces of the residual functional lung. In closed (non-cavitary) necrotizing granulomas, small to moderate numbers of AFB can be observed in foamy macrophages occupying the borders of the necrotic areas, most prominently where breakdown (liquefaction) is occurring. Thus, in most patients with sputum-positive disease, AFB are most numerous at the luminal surfaces of the cavities, i.e., in areas of the granulomas with a patent connection to the airways. In comparison, in sputum-negative patients, the surfaces of the cavities appear inactive, with re-epithelialization over fibrotic tissue. Despite the absence of any visible AFB and the failure to grow bacilli from many of these lesions, MNGs, epithelioid macrophages, and lymphocytes are apparent in small aggregates within the fibrotic tissue. Staining for the presence of $CD3^+CD4^+$ or $CD3^+CD8^+$ T lymphocytes reveals an abundance of these cells within the granulomatous-fibrotic layer and in lymphoid aggregates of the granuloma. Scattered T lymphocytes are also seen within the airspaces. In contrast, a striking absence of $CD3^+$ $CD4^+$ and $CD3^+CD8^+$ T cells is noted in the necrotic zone, as well as at the luminal surface of the cavity [46].

Taken together, these observations suggest that in the cellular granulomatous fibrotic area, adjacent to the necrotic zone, a microenvironment exists where macrophages and T cells co-localize and are free to interact directly, presumably resulting in an efficient immune response capable of inhibiting mycobacterial replication. In contrast, only millimeters away, the luminal surface of the cavity represents a microenvironment within the lung where macrophages do not co-localize with T cells, thus precluding any direct T-cell-macrophage interactions at these sites. This may result in failure to activate the macrophages, thus rendering them permissive to the growth of Mtb. Interestingly, the presence PMNs at the

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luminal surface of the cavity could potentially be associated with down-regulation of the local control of bacillary growth, particularly in advanced disease.

2.3 The alveolar macrophage

In addition to its central role in respiration, the lung serves as a major interface between the host and the external environment and is constantly bombarded by foreign matter, including microbes. Therefore, the lung contains an intricate pulmonary innate and adaptive immune system which serves to protect the host from inhaled foreign particulates [47,48]. Upon inhalation, small (< 5 μm) particulates, such as microbes, are able to avoid the upper airway ciliary beat, the cough reflex, and mucus clearance mechanisms to travel down the trachea and through the bronchi, where they eventually settle in the alveolus. Pulmonary innate immunity at this site is controlled by cellular and soluble components; airway and alveolar epithelial cells and leukocytes join forces with antimicrobial products (e.g. collectins, defensins, lactoferrin, and cathelicidins) secreted into the epithelial lining fluid [49]. Mtb is deposited in this environment and, thus, its interactions in this site are particularly relevant to immune pathogenesis of active TB disease.

The inflammatory response in the alveoli must be tightly regulated in order to protect the delicate gas-exchanging structures from destruction by toxic mediators of the immune system [48,50–53]. AMs are closely associated with the alveolar epithelium and are continuously bathed in surfactant, which is an important immune modulator produced by type II epithelial cells [54]. AMs comprise greater than 95% of the cells found in a bronchoalveolar lavage. Only one to two AMs are found per alveolus, ranging in size from 9–40 μm in diameter [50]. These cells constitute the first line of defense against pulmonary pathogens [55]. The majority of AMs are thought to originate from peripheral blood monocytes that migrated into the airways where they differentiated [14,56]. Alternatively, and more controversial, mononuclear phagocytes present in the lung can divide in the alveolus in response to local inflammatory stimuli [50,57].

AMs are generally considered to be alternatively activated macrophages. While the cells effectively eradicate routinely encountered microbes, they often fail to do so for host-adapted intracellular pathogens such as Mtb. The specific innate inflammatory response produced by AMs upon recognition and uptake of pathogens influences the subsequent adaptive immune system and determines whether the microbe is successfully eliminated with minimal damage to the host [58]. In this regard, AMs have a unique phenotype that includes expression of high levels of a subset of surface PRRs such as the MR, specific Toll-like receptors (TLRs), and scavenger receptor (SR) A [59]. They also have high expression of intracellular regulators, such as nuclear receptor peroxisome proliferator-activated receptor-γ (PPARγ) that respond to infectious agents [60,61] and mediate their clearance [62] and yet do not cause the same marked increase in local tissue inflammatory responses seen in other macrophage populations [58]. Thus, AMs appear to be immunoregulatory cells with high phagocytic activity but relatively poor bactericidal and antigen presentation capabilities, and with the ability to suppress lymphocyte activation [63,64]. They possess a relatively attenuated respiratory burst, increased production of the anti-inflammatory mediators PGE_2 and TGF-β, as well as IL-10, and function to inhibit the amplification of signaling leading to a robust pro-inflammatory response [30,31,65–69]. In this way, AMs protect the delicate lung tissues from destruction by inflammatory mediators [70] or a damaging oxidative burst [71]. In mice, this decrease in oxidative metabolites is partially due to AM production of arginase, which limits NO production [72]. AMs produce less of the intracellular signaling molecule TLR9, which is consistent with a decreased inflammatory response to pathogens [73]. AMs also have decreased production of calcium-dependent protein kinase C (PKC) isoforms and decreased activation of the transcription factor activator protein 1 (AP-1) [74]. Through the increased activity of PPARγ, they also

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function to inhibit the amplification of intracellular signaling leading to a robust pro-inflammatory response by repressing the transcription factors nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB), AP-1, and signal transducer and activator (STAT) [60,75–77].

Pulmonary collectins play an important role in the Mtb-AM interaction. Upon entry into the alveolus, Mtb encounters surfactant, and two surfactant-associated collectins, surfactant protein A (SP-A) and surfactant protein D (SP-D), which regulate the early interaction of the bacilli with resident phagocytes [53,78–80]. SP-A has been shown to enhance PRR activity, increase phagocytosis, alter production of pro-inflammatory cytokines, and decrease reactive nitrogen intermediates (RNIs) and reactive oxygen intermediates (ROIs) in response to stimuli [53,81]. In contrast, SP-D decreases phagocytosis of Mtb by binding to the mannose caps of the Mtb cell wall mannosylated lipoarabinomannan (ManLAM) (see below) and inhibiting the normal interaction with the MR [82]. SP-D-opsonized Mtb that enter the macrophage have reduced intracellular growth due in part to increased phagosome-lysosome fusion [82,83].

In summary, the increased phagocytic potential, combined with a highly regulated and relatively balanced pro- and anti-inflammatory response, makes AMs ideal for preserving the alveolar structure and its essential gas exchange function. Host-adapted intracellular pathogens like Mtb appear to be able to exploit the tightly balanced activity of these cells to enhance their survival and persistence [60,84].

3. Macrophage interaction with Mtb

3.1 Macrophage recognition of Mtb

Macrophages express an array of PRRs and phagocytic receptors that play crucial roles in their recognition and response to pathogens, essential in the initiation of the innate immune response. The divers cell surface receptors are responsible for the generation of combinatorial signals that result in macrophage activation as part of the host defense machinery against invading pathogens [85–87].

I. C-type lectins: Mannose receptor, DC-SIGN, Dectin-1 and Mincle—The MR (CD206) is expressed on AMs [88,89], monocyte-derived macrophages and DCs [90], but not on monocytes [90–93]. It is the predominant C-type lectin expressed on non-activated human macrophages; this selective distribution is different for other mammalian macrophages. Its eight lectin-like carbohydrate recognition domains (CRDs) bind with high avidity and affinity to mannans, notably endogenous unwanted high mannose N-linked glycoproteins, to maintain homeostasis of the host [94,95]. The MR also interacts with microbial pathogen-associated molecular patterns (PAMPs) that contain mannose, found on many different pathogens [96]. The development of these mannosylated PAMPs is thought to be a form of molecular mimicry by which pathogenic microbes, such as Mtb, can evade the immune system through cloaking themselves in molecules that are similar to mannosylated glycoproteins found within the host. Mtb is recognized by the MR via its mannosylated surface structures [97]. MR recognition varies among Mtb strains [98,99], and its involvement has been postulated to be a marker of host adaptation [97]. The MR can discriminate among specific cell wall components of the bacteria due to subtle variations in the degree and nature of mannan motifs. It specifically binds to the mannose caps of ManLAM [100] and to higher order phosphatidyl-*myo*-inositol mannosides (PIMs) found in greater amounts in pathogenic bacteria [101]. MR ligation on non-activated macrophages produces an anti-inflammatory response by stimulating the release of anti-inflammatory cytokines [102] and inhibiting the production of pro-inflammatory IL-12 [103] and ROS [104]. Entry of Mtb through the MR leads to the development of a unique phagosome that

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has reduced fusion with the lysosome [101,105,106]. This phagosome does not acidify normally in part because it does not acquire all subunits of the vacuolar proton ATPase [107,108]. MR engagement by Mtb leads to the induction of PPARγ which, as noted earlier, functions to inhibit a robust pro-inflammatory response. As a prototypic PRR, the MR links innate and adaptive immune mechanisms and, with regards to Mtb, facilitates presentation of lipids and ManLAM through CD1b [90,109–116]. Finally, the MR is thought to play a role in cellular adhesion and fusion, with the formation of MNG, and is thus implicated in Mtb granuloma formation [117].

DC-SIGN (dendritic-cell specific intercellular adhesion molecule 3 grabbin non-integrin) demonstrates high avidity binding to mannosylated glycoconjugates such as N-linked high mannose structures and fucose-containing glycans [101,118–121]. It is present on immature and mature DCs and small sets of macrophages [89,122] and binds to a variety of microbial pathogens [123]. In general, DC-SIGN is not expressed on non-activated human macrophages; however, its expression can be up-regulated upon Mtb infection [124] and induced on macrophages stimulated with IL-4 or IL-13 and granulocyte macrophage colony stimulating factor (GM-CSF) [125]. Mtb ManLAM and PIMs serve as ligands for DC-SIGN on DCs [101,126]. Upon interaction of DC-SIGN with Mtb, the phagocytosed bacteria are targeted for phagosome-lysosome fusion in the antigen presenting cells (APC) [127–129] and DC maturation is impeded [126].

Dectin 1 is a transmembrane PRR expressed on macrophages as well as DCs, monocytes and a subset of T cells [130]. It binds to β-glucan, a common component of the fungal cell wall [131]. Dectin 1 ligation triggers phagocytosis and intracellular signaling cascades, including synergistic interactions with the TLRs, leading to a pro-inflammatory response [132] and a respiratory burst [133]. The role of Dectin-1 in Mtb infection is still unclear. Although no specific mycobacterial ligands for Dectin-1 have been identified so far, this receptor interacts with mycobacteria in concert with TLR2 to produce cytokines such as TNF-α and IL-12p40 [134,135]. Recent studies have proposed additional roles for Dectin-1 in Mtb infection [136,137].

Mincle (Macrophage-inducible C-type lectin; also known as Clec4e or Clecsf9) is mainly expressed on myeloid cells. Mincle expression is very low on non-activatd leukocytes, but is up-regulated after exposure to various inflammatory stimuli, such as cytokines and TLR ligands [138]. Its ligation can induce cytokines such as TNF-α, MIP-2 (macrophage inflammatory protein 1) (CXCL2), and IL-6. Mincle can sense infection by some fungi [139] and can detect an endogenous protein, spliceosome-associated protein 130 (SAP 130), which is released from necrotic host cells. Mincle has recently been shown to serve as a PRR for trehalose dimycolate (TDM) from Mtb [140] but is not essential for controlling Mtb infection in mice [141].

II. Complement receptors and Fcγ receptors—The complement C3 receptors (CR1, CR3 and CR4) and Fcγ (FcγRI, II, III) receptors are major phagocytic receptors on monocytes and macrophages, although their expression and activities vary in a tissue-specific manner. Among the CRs, CR4 is reported to be more prominent in AMs than CR1 and CR3 [142]. In fact, the relative CR expression pattern changes during differentiation with CR3 ≫ CR4 on monocytes developing into CR4 > CR3 on AMs [143]. Thus, complement-opsonized pathogens will interact differently with AMs compared with other macrophage/monocyte populations.

CRs expressed on human monocytes and macrophages play an important role in both opsonic and non-opsonic phagocytosis of Mtb [59,144–146], the latter through interaction of the receptor with surface polysaccharides [147], lower order phosphatidylinositol

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mannosides (PIMs; see below) and glycopeptidolipids [148]. Although CR3 mediates Mtb phagocytosis, the host response following phagocytosis through this receptor is unclear for human macrophages. *In vitro* analysis of peritoneal macrophages from CR3-knockout mice showed decreased uptake of Mtb with equivalent bacterial growth compared to wild type [149]. However, injecting intravenous Mtb into CR3-knockout mice failed to reduce bacterial burden or lessen pathological lesions [150].

Despite the relatively increased expression of Fcγ receptors on AMs, these receptors do not play a role in the initial phagocytosis of Mtb in the absence of opsonizing immune antibody [144] which generally requires activation of the adaptive immune response for specific antibody production, a process that takes several weeks. However, when the bacteria are opsonized with Mtb-specific antibody and phagocytosed, there is enhanced phagosome-lysosome fusion [151], facilitating an increased host macrophage protective mechanism.

III. Toll-like receptors—TLRs are a highly conserved family of transmembrane receptors with an extracellular amino-terminal leucine-rich repeat (LRR) domain that recognizes PAMPs and an intracellular carboxy-terminal tail that is homologous to the interleukin 1 receptor (IL-1R) [152]. The receptor contains a Toll-IL-1R (TIR) domain that forms a scaffold for the assembly of signaling intermediates. TLRs are present on AMs [153], neutrophils [154], lymphocytes [155] and DCs [156] as well as on alveolar epithelial cells [157]. There are at least twelve mammalian TLRs, each responding to a variety of ligands [86,158–161]. After specific ligand binding, TLRs such as TLR2 and TLR4 initiate an intracellular signaling cascade, which generally leads to differential activation of NF-κB and an inflammatory response [86,162,163]. However, several negative regulators, such as interleukin-1 receptor-associated kinase M (IRAK-M), have been identified [164], and pulmonary surfactant can drive increased IRAK-M expression and IL-10 production in macrophages [165]. Signaling can also lead to alternate intracellular cascades, resulting in an anti-inflammatory response [166]. To add to the complexity, TLRs are increasingly found to interact with other cell surface receptors, leading to a modulated inflammatory response [167,168].

TLRs are critical mediators of the immune response to a variety of pathogens, including Mtb [169,170]. TLRs are either expressed on the cell surface (e.g. TLR2 and 4) or intracellularly (e.g. TLR8 and 9) [171]. Mtb and its cell wall components are recognized by several TLRs, including TLR1, TLR2, TLR4, TLR6, and TLR9 [172–176]. Among them, evidence for genetic variants associated with TB susceptibility is most abundant for TLR2, which functions alone or as a heterodimer with TLR1 or TLR6. The 19kDa lipoprotein, lipomannan (LM), and lower order PIMs found on the surface of the mycobacterial cell wall have all been shown to interact with TLR2 [177–179]. TLR expression and function are influenced by the local pulmonary microenvironment. For example, SP-A up-regulates the surface expression of TLR2 on human macrophages, while inhibiting the intracellular signaling of TLR2 and TLR4, which results in a dampened pro-inflammatory response [80].

IV. Scavenger receptors—There are several scavenger receptors (SRs) on AMs with reported roles in antimicrobial host defense, namely SR I and II (SR-AI/II) and the macrophage receptor with collagenous structure (MARCO) [180–182]. In the context of Mtb infection, MARCO is thought to be involved in TLR signaling in response to cell wall components, resulting in increased NFκB activation [183].

V. CD14—CD14 is highly expressed in macrophages and monocytes. It binds to the plasma membrane through a glycophosphatidylinositol (GPI) anchor, although it can also be found in its soluble form in plasma [184]. CD14 recognizes peptidoglycan from Gram-positive bacteria [185] and LPS from Gram-negative bacteria [186]. Other bacterial ligands are

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lipoteichoic acid, lipoproteins and lipoarabinomannan (LAM) from mycobacteria, and mannuronic acid from Gram-negative bacteria [185,187,188]. CD14 has been shown to facilitate the uptake of non-opsonized Mtb by microglia (resident brain macrophages) [189], although by itself is not capable of mediating phagocytosis of the bacilli by human macrophages without the cooperation of other receptors [190] such as TLR2 and 4. Upon ligand binding, macrophage activation leads to inflammatory cytokine production.

VI. The NOD-like receptors—The NOD (nucleotide-binding oligomerization domain)-like receptor (NLR) family members play a major role in innate immunity through inducing an inflammatory response and regulating cell death/survival pathways. They are a second line of recognition, inducing a pro-inflammatory response to bacteria once inside the macrophage [191]. NLRs are mainly expressed in APCs, including AMs and epithelial cells. Most mammalian NOD family members contain 3 distinct functional domains: an amino terminal effector binding domain (EBD), a centrally located NOD, and a carboxy-terminal ligand recognition domain. The NLR family can be divided into four subfamilies depending on the composition of their N-terminal EBD. The differing N-terminal domains are as follows, with subfamily name: acidic transactivation domains (NLRAs), caspase activation and recognition domain (CARD) (NLRCs), pyrin domains (NLRPs), and baculovirus IPA repeat domains (NLRBs). NOD1 and NOD2 are part of the NLRC subfamily and contain a LRR domain, NOD domain, and CARD domains [192]. NOD1 protein is abundantly found in multiple cell types, whereas NOD2 protein expression is abundant in human macrophages [193,194]. NOD1 and NOD2 recognize specific muropeptides found in the peptidoglycan layer of Gram-positive and Gram-negative bacteria [195]. Upon ligation, they activate the mitogen-activated protein kinases (MAPKs) and thereby indirectly allow for NF-κB and AP-1 activation, leading to the production of pro-inflammatory cytokines [196]. NOD2 can directly bind and activate caspase-1 and interact with the NALP1/NALP3 (NACHT, LRR and PYD domain-containing proteins 1 and 3) inflammasome, which causes the activation of caspase-1, an enzyme needed to cleave pro-IL-1β into its active secreted form [197]. Furthermore, there are many reports on the synergistic crosstalk between TLR agonists and NOD2 agonists in pro- and anti-inflammatory cytokine release [198–205].

NLRs have proven to be important in the recognition of a variety of bacterial pathogens, including Mtb [197,206–216]. Recent studies have reported that NOD2 does not have a significant role in controlling Mtb growth during early infection in mouse macrophages [217] but may play a role during late infection [214]. A decrease in pro-inflammatory cytokine production has been observed in mouse NOD2 knockout bone marrow-derived macrophages and naive murine AMs in response to Mtb, without affecting intracellular bacterial growth [214,217]. NOD2 recognizes an N-glycolylated form of muramyl dipeptide (GMDP) found in Mtb [195] and controls the nature of the inflammatory response and subsequent fate of Mtb and *M. bovis* BCG in human macrophages [194].

3.2 The Mtb phagosome

During normal phagocytosis, actin-mediated membrane movements engulf the bacterium into a phagosome with the sequential recruitment of Rab GTPases to the phagosomal membrane, which then recruits the vacuolar ATPases to acidify the phagosomal contents. The membrane ultimately fuses with a lysosome to merge the contents of the acidified phagosome with the lysosomal acid hydrolases. However, during Mtb infection, the phagosome trafficking pathway is altered through multiple mechanisms to disrupt normal host cell microbicidal activities and/or phagocyte effector functions [218–221]. Consequently, once inside the macrophage, Mtb resides in a unique phagosome with an abnormally high pH of ~6.2 and limited fusion of pre-formed lysosomes [222,223]. The early trafficking pattern of the Mtb phagosome includes fusion with early endosomes, since

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both iron [224,225] and glycosphingolipids [226] are found associated with it. However, Mtb ManLAM can inhibit normal calcium increase in the cytosol, causing a disruption in calmodulin complex formation with phosphatidylinositol 3-kinase (PI3K) [222,227,228] and preventing the recruitment of phosphatidylinositol 3-phosphate (PI3P) to the phagosomal membrane [229]. PI3P is a critical lipid intermediate in the recruitment of the vacuolar GTPases to the phagosome [230]. Mtb also inhibits sphingosine kinase which inhibits calcium signaling [231]. Inhibition of full maturation of the phagosome also involves the lack of recruitment of Rab5 effector proteins, such as early endosomal autoantigen 1 (EEA1) [59,232] and hVPs35, to the phagosomal membrane [223,233,234]. EEA1 and Syntaxin-6 are required for the delivery of lysosomal hydrolases, cathepsins and vacuolar ATPases. The Mtb phagosome lacks a specific type III PI3K, required for retention of EEA1 on the endosomal membrane [108,230,235]. Ultimately, these processes result in a failure of phagosome maturation between the Rab5 (an early endosomal marker) [236] to Rab7 (a late endosomal marker) [237] conversion.

ESAT-6/CFP-10 (early secretory antigenic target 6/culture filtrate protein 10), the SecA 1/2 proteins and the eukaryotic-like serine/threonine protein kinase G (PknG) from Mtb interfere with phagosomal maturation [238–241]. Also, several of the Mtb lipoglycans discussed earlier have important effects on phagosome-lysosome fusion. For example, ManLAM modifies trafficking and phagosome-lysosome fusion, as well as decreasing MAPK activation, a critical intracellular signaling molecule [242,243]. The lower order PIMs (fewer mannose molecules), which are found more commonly in less virulent mycobacteria, can enhance phagosomal fusion with early endosomes [179]. Glycolipids such as TDM can interfere with membrane trafficking, preventing phagosome maturation [244]. Recent studies have focused on the utilization of host fatty acid stores and fatty acid metabolism for persistence of Mtb in the phagosome [245–247].

Many studies over several decades have provided evidence that Mtb enters and divides within the macrophage phagosome. However, there continues to be active debate over whether Mtb can also escape from the phagosome into the cytosol [248] and why this would be advantageous to the bacterium or the host. Experiments performed by several groups during the mid 1980s and 1990s showed electron microscopy images where Mtb appears devoid of a phagosomal membrane some days after infection [249–251]. More recently, Brown and colleagues [252] showed that at least some portion of intracellular *M. marinum* (a highly genetically related mycobacterium) escape from the phagosome into the cytosol using an actin-based propulsion system similar to *Listeria;* others have shown that the presence of region of difference 1 (RD1) in the bacterial genome is required for this escape [253]. Similarly, Mtb and *M. marinum* have been shown to be ejected from the amoeba Dictyostelium through an actin-based structure called the ejectosome, using elements of RD1 [254]. Peters and colleagues have recently reported that Mtb can escape from the phagosome of DCs and macrophages after several days in culture [255] in an RD1- and ESAT-6-dependent manner [256]. Several factors have contributed to the discordant results obtained among labs throughout the years regarding bacterial localization and escape. These include the source of cells used, bacterial strain, multiplicity of infection, length of infection, how the bacterial inoculum was prepared, and the microscopy technique used to visualize the phagosomal membrane.

Some studies have proposed that Mtb might be present in the macrophage cytosol several days after infection on its way to escape from the cells and to spread to adjacent cells. Consistent with this, there is growing evidence that virulent Mtb induces cell necrosis by activation of the cytosolic positioned inflammasome in an RD-1 dependent fashion [257,258]. In a very recent study, phagosomal rupture by Mtb and *M. marinum* was closely followed by necrotic cell death of the infected macrophages [259]. Thus, further studies are

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needed to determine whether phagosomal escape is a virulence strategy in terms of intracellular survival or just a consequence of membrane rupture during cell death. Another possibility is that early following infection of macrophages, intraphagasomal Mtb, which possesses an RD-1 dependent ESX-1 secretion system, is able to perforate but not destroy the phagosomal membrane, allowing for a mixture of phagosomal and cytosolic components [260,261]. Finally, it has been postulated that the escape of Mtb from the phagosome to the cytoplasm might be a mechanism by which mycobacterial antigens can be processed and loaded onto MHC I for presention to $CD8^+$ T cells. While the escape of virulent Mtb from the phagosome provides a possible explanation for this form of antigen presentation, an alternative hypothesis is that the phagosome can interact directly with the endoplasmic reticulum [255,262–264].

3.3 The pro-inflammatory cytokine/chemokine response

Local and systemic macrophage production of cytokines and chemokines are central to the cellular response to Mtb infection. These soluble mediators play an important role, not only in controlling early infection, but also during the chronic infection state [265,266]. Of major importance to Mtb infection control are the macrophage cytokines TNF-α, the IL-12 family, IL-6, IL-1α/β and IL-10 [267–272].

TNF-α is an autocrine/paracrine cytokine produced by a variety of cells, including macrophages, DCs, lymphocytes, neutrophils, mast cells and endothelial cells. During Mtb infection, the cytokine functions to regulate the inflammatory response, stimulating the production of IL-1 and IL-6 [273]. It also contributes to the control of Mtb by inducing the production of ROIs and RNIs by macrophages and the early secretion of chemokines [274]. TNF-α plays a crucial role in maintaining granuloma structure and function [275]. Its production is highly regulated because excess TNF-α leads to tissue damage and immunopathology, along with worsened clinical symptoms.

IL-12 represents a family composed of IL-12p40 (homodimer p40 + p40), IL-12 or IL-12p70 (heterodimer p35 + p40), interleukin 23 (IL-23) (heterodimer p40 + p19) or interleukin 27 (IL-27) (heterodimer cytokine with Epstein-Barr virus induced gene 3 [EBI3 or IL-27B] + p28 [known as interleukin 30 (IL-30)]). It is produced by macrophages and DCs after activation by microbial ligands and other cytokines [276] and leads to the development of the T_H1 response during Mtb infection [277,278]. Several studies have shown that IL-12 plays an important role in both innate and adaptative immune responses to Mtb infection. The level of complexity of this family of cytokines during Mtb infection has been highlighted recently [279]. The role of IL-27 during Mtb infection has been focused on during the past decade. This cytokine promotes both pro- and anti-inflammatory responses. Together with IL-12, it initiates the T_H1 response, enabling the release of T cell IFN-γ during infection [280,281], although it can contribute to uncontrolled inflammatory responses over time [282,283]. A recent study has shown that IL-27 inhibits human macrophage activity during Mtb infection [284].

IL-23 is produced in response to interleukin 17 (IL-17) from T_H17 CD4 T cells, and recent studies have demonstrated that the IL-17/IL-23 pathway may play a key role in controlling mycobacterial infections [285–287] by enhancing the development of protective and regulatory immune responses. IL-17 promotes the development of antimicrobial responses, chemokine production and the recruitment of inflammatory cells [288,289]. IL-23 is required for the maintenance of T_H17 responses against Mtb by inducing IL-17 production by memory T cells [290,291]. In general, the IL-17 family is crucial in keeping the balance between bacterial killing and minimizing tissue damage.

IL-6, produced by macrophages and a variety of other cell types [292,293], has both pro- and anti-inflammatory effects. It is produced during early Mtb infection and is critical for early protective mechanisms, such as cytotoxic T cell differentiation.

IL-1β is a product of inflammasome activation and regulates a number of processes important in controlling Mtb infection, including iNOS production [294], phagosomal acidification and maturation, up-regulation of adhesion molecules [295] and regulation of a variety of enzymatic activities, such as cyclooxygenase and phospholipase A [296,297]. It is essential in maintaining resistance against Mtb infection.

IL-10 is produced by monocytes, macrophages, DCs, and T regulatory cells (T regs) [298,299]and functions as an immunomodulatory cytokine. During Mtb infection, it is thought to suppress inflammation to limit tissue damage. It inhibits pro-inflammatory cytokines (IL-1, IL-6, IL-12, IL-8 and IFN-γ) [300–305]and chemokines (CCL (C-C motif ligand) 3, CCL4 and CCL5) impacting cell recruitment, the generation of oxidants [300,306,307] and antigen processing and presentation [308]. Recent studies have shown that IL-10 may interfere with phagosome maturation in human macrophages [309].

The production of chemokines is essential for the recruitment of inflammatory cells to the site of infection. The early recruitment of macrophages is an important step in controlling the infection [310]. Mtb is a strong inducer of chemokines that participate in protective and immunopathogenic host responses during Mtb infection [311,312]. Several studies have focused on the expression of inducible chemokines after Mtb infection of macrophages *in vitro* [313]. The results have shown that human macrophages produce CCL2, CCL3, CCL4 and CCL5 (MCP-1 (monocyte chemoattractant protein 1), MIP-1a, MIP-1b and RANTES (regulated upon activation normal T cell expressed and secreted)) in response to virulent mycobacterial strains [314,315]. MIP-1a, MIP-1b and RANTES induce T cell activation and proliferation [316] and activation of macrophages [317], and MIP-1a promotes T cell differentiation [318]. Several studies have shown the presence of MCP-1, MIP-1a, RANTES and IP-10 in the serum and bronchoalveolar lavage of TB patients [314,319]. AMs produce more CCL2, CCL3, CCL4, IP-10 (CXCL (C-X-C motif ligand) 10) and CCL5 than monocytes after Mtb infection [314]. These results also suggest that chemokines interacting with CCR (chemokine C-C motif receptor) 1, CCR2 and CCR5 play a role in the influx of cells to the site of infection, thereby impacting granuloma formation [320]. Expression of chemokines by macrophages can influence TNF-α production by macrophages after Mtb infection, specifically CCL2, CCL3, CCL4, CCL5, CXCL10 and CXCL13 [321]. Chemokine receptor expression may also be affected by TNF-α production. Therefore, TNF-α may influence the chemokine network expression during Mtb infection, which can indirectly impact granuloma formation. Also, some mycobacterial cell wall components regulate the induction of chemokine secretion by macrophages [322].

3.4 Macrophage death during Mtb infection

The ability to regulate the death of infected host cells is important during many microbial infections. The host regulates cell death pathways to enhance the induction of immunity and to control pathogen dissemination, while the pathogen uses many strategies to manipulate host cell death pathways to enhance its survival. Apoptosis (programmed cell death) plays a critical role in homeostasis and embryonic development. Apoptosis is an energy-dependent process mediated by the caspase cascade that results in the formation of apoptotic vesicles, organelles where the cell contents are kept inside a plasma membrane. Apoptotic cells, including macrophages, are degraded by adjacent macrophages through efferocytosis, which has recently been shown to function as a host defense mechanism for Mtb [323]. Apoptosis represents primarily an anti-inflammatory and immunoregulatory process [324]. However, a recent study has shown that apoptosis may induce a pro-inflammatory response upon

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macrophage phagocytosis of Mtb-triggered apoptotic neutrophils [325]. In contrast to apoptosis, necrosis is a relatively energy-independent process that does not involve caspase activation. Necrosis elicits a pro-inflammatory response as the cell membrane is permeabilized and the cell contents are extruded. It has long been thought to be a non-specific response to excessive stress, tissue damage or microbial invasion of the cell. However, it may in fact follow a series of programmed steps [326]. Macrophage necrosis in the TB granulomas appears to be driven by the bacillary load and the proapoptotic cytokines produced by the infected and associated uninfected leukocytes surrounding bacilli-infected cells in the granuloma, and is a hallmark of the host granulomatous response to Mtb infection [327].

Finally, regarding inflammasome-related cell death types, pyroptosis and pyronecrosis can both occur with microbial infection. They are considered to be pro-inflammatory and are a way to increase the recruitment of immune cells to the site of infection, although they can be detrimental to the host if excessive inflammation is elicited. While it has been shown that Mtb is able to activate the NLRP3 inflammasome through ESAT-6 [328–330], evidence is lacking for whether Mtb can induce pyroptosis and pyronecrosis in the macrophage.

In summary, cell death has been associated with both Mtb virulence and host defense. In the granulomas, where leukocyte necrosis can be extensive, macrophage death is closely associated with the pathology and tissue damage of chronic TB disease. The relative contribution of various specific cell death pathways during the course of Mtb infection *in vivo* (primary infection, latency and reactivation) awaits further study.

3.5 Chronic inflammation and fibrosis

The progression of Mtb infection to active disease leads to a chronic inflammatory state and eventually tissue necrosis, fibrosis and remodeling. Macrophages play a central role in these processes by secreting cytokines and inflammatory mediators, such as prostaglandins, and producing enzymes and growth factors that promote connective tissue degradation, fibrosis and angiogenesis. The matrix metalloproteases (MMPs) are important mediators of extracellular matrix proteolysis and tissue. Various types of collagenases (MMP1, MMP13), elastases (MMP12) and gelatinases (MMP2, MMP9) are members of the MMP family. Each of these enzymes degrades specific components of the underlying connective tissues associated with granulomas in the lung or other infected organs [331]. The interaction of these MMPs with their respective tissue inhibitors of metalloproteinases (TIMPs) in response to Mtb infection is an important regulatory component of immune pathogenesis at the site of Mtb infection [332].

During TB, Mtb promotes destruction of the lung extracellular matrix to cause necrosis, liquefaction and ultimately formation of cavities, where Mtb can proliferate and spread from the interstitium to the airways [46]. To generate cavities, Mtb requires the activity of MMPs [333,334]. The MMP:TIMP ratio is critical in regulating the proteolysis of tissue and controlling tissue damage. In this regard, several studies have assessed MMP expression in response to Mtb infection *in vitro* and in animal models. Expression of MMP-1 and MMP-9 is up-regulated in human THP-1 cells after stimulation with mycobacteria [335,336] or LM via TLR and CD14 signaling [337]. Mtb infection can up-regulate MMP-1, −3, −7 and −10 as well as the related A disintegrin and metalloproteinases (ADAMs) in primary human macrophages [338]. In addition, MMP-1 up-regulation was higher in Mtb-infected primary human cells, compared to *M. bovis* BCG, while MMP-7 production was equivalent. In a rabbit model of pulmonary TB, the transcript levels of MMP-1, 2, 3, 9, 1, 13 and 14 were found to be elevated during the active disease process, and characterized by tissue necrosis and cavitation [339]. Consistent with this finding, a fibrotic capsule surrounding the lung granulomas of rabbits with active disease was observed, as demonstrated by positive

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staining for collagen deposition [339]. In humans, the concentrations of MMP-1 and –3 were elevated in induced sputum and bronchoalveolar fluid of TB patients compared with non-TB patients [340]. A recent study has correlated the presence of MMPs, TIMPs and pro-inflammatory cytokines in human TB pleuritis patients, concluding that levels of MMP-1, –7 and –9, as well as TIMP-3, *in vivo* correlate with production of the pro-inflammatory cytokines IFN-γ and IL-6 [341]. Histologic studies on human TB granulomas have shown that MMP expression occurs at the site of Mtb granuloma formation; specifically, MMP-1 and –7 are expressed by epithelioid cells and giant cells [338], while MMP-9 is produced by the pulmonary epithelial cells [342]. Although the literature is robust for the importance of MMP-9 during Mtb infection, its biological relevance compared with other MMPs remains unclear.

4. Mtb strain diversity

4.1 Strain specific macrophage activation

Recent reports have indicated that different clinical Mtb strains can induce differential host immune responses, leading to variable levels of pathogenesis in animal models [343–346]. Indeed, the view of pathogenic mycobacteria as a relatively homogeneous clonal population with minimal functional genetic diversity has been challenged by molecular genotyping [343,347,348] and whole genome sequencing of members of the Mtb cluster (MTC) [349,350]. An analysis of diverse Mtb and MTC strains show phylogenetically-constrained patterns of bacterial gene expression, including lineage-, genotype-, and strain-specific signatures. These observations suggest a functionally heterogeneous population of pathogenic mycobacteria, highlighting the impact of genetic diversity [351]. In the absence of significant horizontal gene transfer, lineages of Mtb may define discrete evolutionary trajectories bearing distinct phenotypic properties [352,353]. Thus, biomedically relevant traits may be non-randomly distributed in the bacterial population along clonal lines [354,355]. Recently, phylogenetically diverse Mtb strains have been shown to exhibit markedly different virulence and pathogenesis phenotypes in macrophage *in vitro* culture and animal infection models [344]. Moreover, a number of specific Mtb strain families have been reported to show an unusual degree of outbreak or epidemic potential, drug-resistance or marked tissue tropism in humans [356–358]. Thus, there is evidence of genetic variation and associated phenotypic diversity in Mtb. However, there have been few in-depth studies to examine the mechanistic underpinnings for these clinically and epidemiologically important associations.

Recent studies suggest that the differential induction of host macrophage activation and consequently host immunity plays an important role in this Mtb strain-dependent diversity of pathogenesis [343,344]. One study has shown that a W-Beijing strain was able to replicate in cultured human macrophages at a 4–8 fold higher rate, compared to other unrelated Mtb strains [359]. In mice infected with a W-Beijing isolate (HN878), the bacillary load in the lungs was 10-fold higher than in mice infected with a non-W-Beijing isolate (CDC1551) [344]. Reduced survival of HN878-infected mice correlated with relatively weak pro-inflammatory immune cytokine production following *in vitro* macrophage infection (*e.g.* TNF-α). This differential immune response was attributable to the presence of an Mtb-specific phenolic glycolipid (PGL-tb) in HN878 [360]. The differential cytokine responses of macrophages exposed to lipid extracts prepared from HN878 or CDC1551 were similar to those stimulated by the intact bacilli, while other cellular fractions did not induce a differential response [361]. When a single gene necessary for the synthesis of PGL-tb (polyketide synthase, *pks1-15*) was disrupted (HN878*pks1-15::hyg*), a less virulent phenotype was obtained; complementation of the PGL-tb phenotype restored virulence. In another report, hypoimmunogenic strain CH, responsible for an outbreak in Leicester, was linked to a specific chromosomal deletion

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(Rv1519) [362]. While some of the microbial factors driving immunologic phenotypes have been shown to be strain-specific, a study describing cytokine responses between broader, phylogenetically defined "ancient" and "modern" lineages, noted reduced *in vitro* human macrophage responses in the latter group, possibly lending selective advantage in the context of rapidly expanding human populations [363]. A study by Lopez *et al.* found that genetically distinct Mtb strains (representing the four major lineages found globally) resulted in a spectrum of immunopathologies in a murine intratracheal infection model [343]. Macrophage infections with various Mtb strain types induced a differential pattern of cytokines *in vitro* [364]. Dormans *et al.* found in a murine model that 19 different Mtb complex strains from 11 major genotypes produced responses that varied widely with respect to virulence, pathology, bacterial load and delayed-type hypersensitivity [365]. In support, a study by Homolka *et al* noted that genetic diversity appeared to have functional consequences during intracellular infection of bone marrow-derived macrophages, where transcriptomic profiles were lineage-specific [351].

These studies and others show that subtle genetic alterations among clinical Mtb strains can lead to variance in the ability to induce immune responses in the infected host [366]. In this regard, recent studies have compared the immune response to the clinical Mtb isolates HN878 and CDC1551during infection of New Zealand White (NZW) rabbits. These studies and others demonstrate that selection of the Mtb strain used for infection determines whether the animals control the infection and establish latency (e.g. CDC1551) or fail to control infection with development of progressive cavitary disease (e.g. HN878) [367,368]. Infection of rabbits with the HN878 strain leads to the formation and maturation of all of the granuloma types discussed earlier, thereby mimicking human TB [367]. Gene arrays and RT-PCR have shown that, as granulomas progress, the nature of macrophage activation evolves as well [367,369].

4.2 The mycobacterial cell envelope

Induction of differential immune responses to Mtb strains is due in part to differences in the nature of the mycobacterial cell envelope, which plays a critical role in the survival of bacteria within macrophages [370,371]. The cell envelope consists of an innermost plasma membrane, followed by a peptidoglycan-arabinogalactan layer, a thick mycolic acid layer, and then an outer layer consisting mainly of surface carbohydrates and proteins [372]. Several of the components of the Mtb cell wall have been shown to be immunomodulatory, including the lipoglycoconjugates: LAM, LM and PIMs. These lipoglycoconjugates are biosynthetically and structurally related and are thought to be located both in the innermost layer as well as exposed on the surface of the bacteria. The surface-exposed carbohydrate moieties are, thus, available to interact with lectin components of the innate immune system, such as the MR and SP-D [83,98,100,145].

PIMs vary in their number of mannose sugars and acyl chains, which affect their interaction with cell surface receptors, such as the MR and DC-SIGN [101]. These variations confer subtle differences on the immune response. In general, LMs are thought to be pro-inflammatory molecules with variable effects on the immune system based on the species of origin. TNF-α production is robust for *M. smegmatis* LM-stimulated human macrophages, but not for LM from Mtb. This diversity was found to be due in part to differential microRNA regulation [373] in response to subtle variations in the structure of the molecule, such as the presence of increased succinates in *M. smegmatis* LM [374]. These results are consistent with the decreased TNF-α response seen in virulent mycobacteria infection compared to nonpathogenic mycobacteria [375]. Similarly, it has been shown that LM stimulates macrophages through different receptors based on the number of acyl chains with tri-acylated LM interacting through TLR2/TLR1, while tetra-acylated LM interacts through TLR4 [376].

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The LAMs are the largest, most complex lipoglycans, built upon LM with branches of arabinans followed by species-specific 'caps,' which are the terminal molecules on the end of some of the arabinan branches. These caps can be 1-, 2- or 3- linked mannoses, known as mono-, di- or tri-mannoside caps (ManLAM), phosphatidyl-*myo*-inositol caps (PILAM), or uncapped (AraLAM from *M.chelonae*) [377]. Even within Mtb strains, there is variability in the number and type of caps in mycobacteria. For example, pathogenic Mtb laboratory strains (Erdman, $H_{37}R_v$) have a higher proportion of α 1–2 linked di-mannoside-capped ManLAM, while less pathogenic strains ($H_{37}R_a$) and species (*M. marinum* and *M. avium*) have relatively more mono-mannoside-capped ManLAM [378], and nonpathogenic *M. smegmatis* has infrequent PILAM [379]. ManLAMs are also important regulators of the immune response that assist in bacterial survival. As with the other lipoglycoconjugates, the interaction of ManLAM with the host immune system depends upon subtle variations in structure. For example, the number of mannose caps and degree of mannose capping can affect the cell receptor that interacts with the bacteria, since ManLAM from three different Mtb strains, all known to have mainly di-mannosyl groups on ManLAM, showed variations in their binding to the MR [99]. Thus, subtle variations in structures of these lipoglycans are important in determining the interaction of the bacteria with specific cell receptors and, ultimately, the nature of the host immune response [380]. We have recently shown this to be the case for a set of clinical Mtb isolates found to naturally possess a truncated ManLAM structure [99].

5. Conclusions

Our current understanding of the role of macrophages in TB, although incomplete, clearly demonstrates the central role these cells play both in the host protective immune response and control of infection, and in the maintenance of chronic infection and its associated tissue damage and pathology. As we gain more knowledge about macrophage responses in the context of organ-specific microenvironments, our understanding of the molecular details underlying the pivotal Mtb-macrophage interactions that occur during TB infection will become more defined. In future studies, it is critical that we better understand these interactions during the entire spectrum of TB from primary infection, dissemination, microbial growth within granulomas, control of infection and latency and re-activation disease. It is clear that the nature of the macrophage receptor recognition, signaling, inflammation and antigen presentation pathways differ during different stages of infection and disease, and that the nature of the infecting Mtb strain also contributes to this diversity of responses. Since recent publications have highlighted the major differences in immune response among humans and different animal models, future studies must focus on comparative biology among mammalian hosts with an eye towards the use of animal models that better recapitulate what is seen in human disease. In addition, an important future focus will be studies of human clinical samples and the use of platform technologies to maximize our understanding of human TB in order to develop rational approaches to find critically needed new biomarkers, therapies and vaccines.

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