Review Article

New Aspects in Immunopathology of *Mycobacterium tuberculosis*

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Our understanding of tuberculosis (TB) pathology and immunology has become extensively deeper and more refined since the identification of *Mycobacterium tuberculosis* (MTB) as the etiologic agent of disease by Dr. Robert Koch in 1882. A great challenge in chronic disease is to understand the complexities, mechanisms, and consequences of host interactions with pathogens. TB, caused by MTB, is a major health problem in world, with 10 million new cases diagnosed each year. Innate immunity is shown playing an important role in the host defense against the MTB, and the first step in this process is recognition of MTB by cells of the innate immune system. Several classes of pattern recognition receptors (PPRs) are involved in the recognition of MTB, including toll-like receptors (TLRs), C-type lectin receptors (CLRs), and nod-like receptors (NLRs). Among the TLR family, TLR1, TLR2, TLR4, and TLR9 and their down streams, proteins play the most prominent roles in the initiation of the immune response against MTB. Beside of TLRs signaling, recently the activation of inflammasome pathway in the pathogenesis of TB much appreciated. Knowledge about these signaling pathways is crucial for understanding the pathophysiology of TB, on one hand, and for the development of novel strategies of vaccination and treatment such as immunotherapy on the other. Given the critical role of TLRs/inflammasome signaling in innate immunity and initiation of the appropriate adaptive response, the regulation of these pathways is likely to be an important determinant of the clinical outcome of MTB infection. In this review paper we focused on the immune response, which is the recognition of MTB by inflammatory innate immune cells following infection.

1. Introduction

Despite the availability of effective and inexpensive therapy, TB is considered as one of the leading causes of death from an infectious disease worldwide [1].

For long time it is believed that TB is a major public health problem in the world, with 10 million new cases diagnosed each year, causing a death toll of 2 million victims. However, from the estimated 2 billion individuals that have been initially infected with mycobacterium tuberculosis (MBT), only 5% to 10% develop symptomatic TB [2, 3]. The reason of the susceptibility of individual to the TB is not well described. The role of inborn variability in susceptibility to TB has been described [4]. This finding indicates that at least some individuals display an effective immune response against the MTB and that this plays an important part in determining the disease [5].

In addition, this episode in young infants known to have immature adaptive immunity also suggests that the innate host defense is an important arm of antimycobacterial host defense [6]. Thus, understanding the immunologic pathway and mechanism leading to inflammatory process by MTB may lead to better therapeutic approaches in controlling the TB. In this review paper we will cover the role of immune cells and inflammatory mediators which might be playing role in the pathogenesis of TB. We will also outline the role of both Th1 and IL-17 response against TB. Finally, we will discuss the ability of MBT to activate innate immunity such

as toll-like receptors (TLRs) or inflammasome pathways and how these receptors contribute to inflammation by signal transduction pathways.

2. Immunology of MTB

The human immune response to TB is a complex reaction to infection with a vigorous pathogen. This interaction between cellular immune system takes place in a fluid environment containing a wide variety of inflammatory mediators, and these various factors have a large impact on the body's ability to successfully contain infection. In the last few years in vitro and animal studies have begun to be complemented by human studies using material obtained by BAL from TB patients and from control volunteers.

Here, we tried to summarize the information available on host immune response to the TB, complexity of host-pathogen interaction and highlight the importance of signal transduction mechanisms involved in the pathogenesis of TB.

In these regards emerging data emphasizes that the host defenses against MTB need an immune cellular response usually via activation of Th1/Th17 [7, 8]. For long time it has been shown that T-cell subsets based on immune responses have been the delineation of the T helper 1/T helper 2 which provides a framework for understanding how the immune system directs responses to the diversity of pathogens and stimuli. The two major subsets of CD4 T-helper cells, Th1 and Th2, have different patterns of mediators production, playing different roles in immune responses.

Th1 is characterized by TNF-α, IL-2, INF-γ production, and Th2 cells by IL-4, IL-5, and IL-13 release. Th1-type cytokines stimulate macrophages and cell-mediated reactions (CMRs) important in resistance to infection with intracellular pathogens, and in cytotoxic and delayed-type hypersensitivity (DTH) reactions. Th2 cells release IL-4, IL-5, IL-6, IL-10, and IL-13; Th2-type cytokines encourage diverse antibody production and are, therefore, commonly found in association with antibody responses that are important in combating infections with extracellular organisms [9]. Th1 and Th2 cells are mutually inhibitory to each other; IL-10, a product of Th2 cells, inhibits the development of Th1 cells by acting on antigen-presenting cells, whereas IFN-γ, a product of Th1 cells, prevents the activation of Th2 cells [10, 11].

In this line it has been demonstrated that defects in the generation of the Th1 cell effector INF-γ resulted in susceptibility to TB infection [12, 13]. MTB initially infects inflammatory cells especially macrophages and dendritics cells [14]. MTB is surrounded by a lipid-rich outer molecules as a capsule which protects it from the toxic radicals and hydrolytic enzymes produced as a defense by macrophages and inflammatory cells [15]. Pathogenic mycobacteria can spread into neighboring resting macrophages and other cells considered for replication. Macrophages, activated by exposure to inhaled particulates, possess potent microbicidal activity which can kill bacilli and arrest TB infection, but usually they cannot eliminate infection entirely [16]. Other critical mechanisms of antimycobacterial immunity include

the destruction of infected cells by cytolytic T lymphocytes has been documented [17, 18].

While CD4$^+$ T cells are generally acknowledged to be crucial, the contribution of other T-cell subsets including gamma/delta T ($\gamma\delta$ T) cells, Th17 cells, and even conventional CD8$^+$ T cells has been described by many investigators [19–21]. In this line an initial growth of MTB results in a delayed type hypersensitivity response which is characterized by the formation of small necrotic lesions with solid caseous centers in infected area [22]. MTB multiplication is shown that restricted while encapsulated in these granulomatus lesions. Granulomas (lesions) consist of T lymphocytes and mononuclear phagocytes of various levels of maturation and stimulation [23]. After starting delayed-type hypersensitivity (DTH) and tubercle formation, stimulation of macrophages by CD4$^+$ T$_{DTH}$ cells enables the macrophages to kill bacilli inside of the tubercle lesions. Macrophage activation appears to be a central step of acquired resistance against MTB [24].

Macrophage activation is achieved by T lymphocytes which are the principle mediator of cell-mediated immune response against MTB. CD4$^+$ T cells are primarily helper T cells which secrete different types of interleukins involved in the activation of macrophages [25]. In the DTH response to MTB, CD4$^+$ T cells predominate over CD8$^+$ T cells which are primarily cytolytic cells that lyse specific target cells. Helper T cells are required to recruit and activate new monocytes and macrophages to the tubercle lesions. As indicated earlier, Th1 cells produce the cytokines IFN-γ and IL-2, which are important for activation of antimycobacterial activities and essential for the DTH response. IFN-γ specifically activates macrophages and stimulates them to ingest and kill mycobacteria more effectively [26]. Macrophage activation by cytokines provides only a partial explanation for immunity to MTB. The presence of an MHC Class I-restricted response to mycobacterial infection has been described in several T lymphocytes. CD8$^+$ T lymphocytes contribute to macrophage activation by producing IFN-γ [26]. CD8$^+$ T cells also may have capability as a cytolytic functions which enable them to recognize mycobacterial antigens presented by MHC Class I molecules on the surface of infected macrophages. CD8$^+$ cytotoxic T lymphocytes (CTLs) are thought to be required to release intracellular MTB residing in infected macrophages [27]. CTLs with specificity for MTB antigens have been identified in the murine model of tuberculosis. In this line it has been shown that exogenous antigen can gain access to Class I processing and presentation pathway and elicit a CD8$^+$ T-cell response in vivo.

Besides, it has been demonstrated that MTB has the ability to survive within macrophages, providing metabolic antigens for processing and presentation with Class I molecules on the macrophage surface [26]. It has been suggested that MTB may be able to avoid processing within the phagolysosomal environment and in doing so antigen may enter the endogenous antigen-processing pathway and be presented to CD8$^+$ T cells [28].

Thus, now it has been proposed that CD4$^+$ T cells may also play a role in host defense against MTB infection via cytolytic activity [29]. In this regard, CD4$^+$ T cells may also

be capable of lysing nonactivated, infected macrophages and subsequently be taken up by activated macrophages which can destroy the mycobacteria. The presence of CD4+ T cells has been detected only in vitro human peripheral blood samples [30].

Gamma/delta ($\gamma\delta$) T cells have been shown playing an important role in host defence against MTB. In particular, these cells can lyse macrophages containing mycobacteria and are an early source of IFN-γ [31]. They might have a role in the initial, innate immune response to MTB, because their population is expanded by mycobacteria and mycobacterial products in tissues. Interestingly, it has been shown that after subcutaneous and aerosol immunization of mice with mycobacteria, a significant proportion of the mycobacteria-reactive gamma/delta T cell population was activated [32]. These cells are also able to release IFN-γ which may be an important trigger at initial stages of immune response against TB.

Natural killer (NK) cells may also play an important role in the host immune response to MTB. NK cells shown are able of lysing host cells infected with MTB pathogens indicating functional similarities with specific cytolytic T lymphocytes [33, 34].

The role of T_{reg} cells in immunity to MTB has not yet described, however based on studies in humans have shown that numbers of T_{regs} are augmented in the blood and at infection sites in patients with active form of the TB [35–37].

Finally the role of Th17 cells and IL-23 recently has been emerged. For example, it has been shown that, by TB aerosol infection, the absence of IL-23 leads to ablation of the Th17 response and significant loss of IL-17mRNA expression in the lung [38]. These data demonstrate that IL-23 is essential to the expression of both the Th17 population and the IL-17 response to the TB infection. Regardless of the specific role of IL-23, it is likely that this cytokine will be required for optimal Th17 responses to mycobacterial infection in humans. It has been shown that IL-17 is recognized as an inflammatory cytokine capable of inducing chemokine gradients and initiating inflammation, particularly in the lung [39–41]. IL-17 and IL-23 induced neutrophils influx and hemostasis into the lungs of MTB infected mice [42].

It is clear therefore that IL-23 and IL-17 are acting in a complex manner in the control of TB-induced inflammation. This is not so surprising as IL-17 can act as a mediator of macrophage accumulation [43] and mediated of induction of CXCL chemokines containing IL-17-associated promoter elements [44, 45].

Thus, these data suggest that during TB infection IL-17 can act to mediate accumulation of both polymorphic and mononuclear cells.

2.1. Cellular Immunity to MTB

2.1.1. Macrophages and Monocytes. Macrophages are important effector cells in immunity to intracellular bacteria but at the same time are exploited as host cells by a number of microorganisms such as MTB. Macrophage cell death is thought to play a major role in TB pathogenesis [46].

Macrophages are important effector cells in immunity to intracellular bacteria but at the same time are exploited as host cells by a number of microorganisms such as MTB. As indicated earlier, MTB, the causative agent of TB, is a facultative intracellular parasite of macrophages. In order for MTB to establish infection, it must first entier into alveolar macrophages following the inhalation of infectious aerosols. Macrophages are able to engulf inhaled bacteria by using a variety of phagocytic receptors. A number of different phagocytic receptors have been implicated in MTB entry to macrophages such as complement toll-like and mannose receptors [47–49].

It has been reported that MTB infection is accompanied by nonspecific inflammatory responses regulated by inflammatory mediators produced by macrophages which are activated by various signals [50, 51] which is followed by delivering the bacteria to phagolysosomes as an important mechanism to remove intracellular pathogens. After phagocytosis, nonpathogenic MBT is degraded by the acidification of the phagosomal compartment that contains hydrolases active at low pH. Keys to the virulence of MTB are its capacity to prevent the incorporation of the ATP/proton pump into the phagosome membrane and to restrict the fusion of this vacuole with lysosomes [52].

In this line it has been shown that, in resting macrophages, pathogenic MBT blocks phagosome maturation to assure intracellular survival and replication [53–55]. However, in activated macrophages by IFN-γ, the maturation of phagosome was blocked, possibly through induction of and intersection with the autophagic pathway. Within the phagolysosome, MTB is deprived of essential nutrients such as iron and exposed to microbicidal effectors generated by IFN-γ-activated macrophages such as antimicrobial peptides (AMPs) and reactive oxygen or nitrogen intermediates, the products of NADPH oxidase and nitric oxide synthase (NOS2), respectively [56–58]. Besides, it has been shown that macrophages may respond by undergoing TNF-α-mediated apoptosis and possibly through other cell-death pathways [59, 60].

Apoptosis contributes to host defense by removing the MTB growth, by direct antimicrobial effects, and by packaging MTB bacilli and antigens in apoptotic bodies. The subsequent engulfment of these apoptotic bodies by newly recruited macrophages and DCs promotes the eradication of infection and the induction of the adaptive immune response [61].

2.1.2. Polymorphonuclear Cells (PMN). Neutrophils are the cells rapidly recruited to sites of MTB infection, where they phagocytose bacilli effectively [62]. In this line it has been shown that neutrophils are professional phagocytes cells that play important roles in many infections, and increased amounts of neutrophils are observed in the BAL fluid of patients with pulmonary MTB [63]. Moreover, animal studies have also described acute and chronic neutrophil accumulation during MTB infection [64, 65], which could be suggested to speculation on various roles for neutrophils in the development of TB [66]. Nevertheless, the exact

role of neutrophils in the pathogenesis of MTB infection in humans is still not completely understood. There are few reports describing increased neutrophil populations and their phagocytic activity in patients with active pulmonary MBT [67].

2.1.3. Dendritic Cells Response. The critical role of DCs in the pathogenesis of MBT has been extensively described. In this regard, different subsets of DCs are most potent APCs of the innate immune system that have the ability to stimulate quiescent, naive, or memory T lymphocytes [68]. DCs exist at various stages of development, activation, and maturation that are defined by distinct phenotypic and functional modalities [69]. After inhalation, MTB is phagocytosed by alveolar macrophages and DCs resident in the alveolar space of lungs. It has shown that DCs are able to efficiently travel to local lymph nodes and successfully present antigen to T cells, which generates effective cell-mediated immunity [70, 71]. Translocation of MTB to the lymph node by infected DCs is an important precursor to T-cell activation [72, 73]. Upon exposure of DCs to MTB, IL-12p70 and IL-23 are induced which are playing critical role in the pathogenesis of TB [74–76]. Besides, it has been shown that DCs undergo cell death after infection with MTB in vitro, just as macrophages, and could help by this way the protection of host against TB [77].

2.2. Humoral Immunity to MBT. As indicated earlier IFN-γ, an inflammatory cytokine stimulates the antimicrobial activity of macrophages and regulates their antigen presentation through the MHC Class II molecules by upregulating their mRNA and protein expression [78]. As well, IFN-γ can induce autophagy, a mechanism that plays an important role in the innate immunity against intracellular microorganisms [79, 80]. MHC type II-restricted CD4$^+$T cells, MHC class I CD8$^+$T cells, and macrophages are important in the protective immunity against MTB where a decrease of the number or function of these cells results in the reactivation of the infection [81], and γ/δ T cells play an important role in the protective immune response to tuberculosis (TB) [82].

MTB is an obligatory aerobic, intracellular pathogen, which has a predilection for the lung tissue rich in oxygen supply. The MTB enters the body via the respiratory system route. The bacilli spread from the site of initial infection in the lung through the lymphatics or blood circulation to the other parts of the body, the apex of the lung, and the regional lymph node being [83, 84].

Extrapulmonary TB of the pleura, lymphatics, bone, genitourinary system, meninges, peritoneum, or skin occurs in about 15 percent of TB patients [85, 86].

Immunity to MTB associated with Th1 activity involves TNF-α, IFN-γ, and IL-12 releases. Neutralization of TNF-α leads to reactivation of disease [87] and genetic defects of the receptors for IFN-γ or IL-12 lead to increased susceptibility to MTB (see Figure 1) [88].

Initiation of the innate immune response starts with pattern recognition of microbial structures called pathogen-associated molecular patterns (PAMPs). Recognition of PAMPs is performed by germline-encoded receptors expressed mainly on immune cells termed pattern recognition receptors (PRRs).

The first step in understanding the mechanisms of recognition of pathogenic bacteria is a solid knowledge of the structure of the cell wall of the microorganism, which is the first structure to come in contact and to be recognized by the cells of the immune system. It has been demonstrated that dectin and TLR4 are playing role in induction of IL-17 by TB [89]. The cytokine IL-10, which is generally secreted by TH2 cells, affects macrophages by suppressing cytokine production, and thereby downregulating TH1 cell activity and proliferation, and one study suggests that IL-10 plays a central role in enhancing the survival of MTB within macrophages [90]. It has been shown in a variety of studies that both cytolytic T lymphocytes and IFN-γ-activated macrophages are necessary for conferring protective immunity against MTB [91]. As a result these are the immunological pathways that must be focused on in developing an efficacious vaccine to tuberculosis. The Th1 pathway of the immune response including CTL activation is best stimulated by antigens that have been synthesized and degraded inside the cell and presented on the cell surface with MHC Class I. IFN-γ is an important cytokine for immune protection, but, in excess, it is also a key mediator of immunopathology. Massive activation of macrophages within tubercles by IFN-γ results in concentrated release of lytic enzymes. These enzymes destroy neighboring healthy cells and create circular regions of necrotic tissue [92].

3. Role of Signal Transduction Pathways in the Pathogenesis of MBT

3.1. Role of Toll-Like Receptors (TLRs) in Pathogenesis of MTB. Toll-like receptors (TLRs) play a critical role in both innate resistance and the initiation of adaptive immunity to infectious agents [93–96]. So far fifteen functional TLRs have been identified in mammals, and they are playing important role in specific recognition of pathogen associated molecules [97]. Upon ligand binding to the receptors, TLRs initiate a cascade of events leading to the transcription of NF-κB-dependent genes, mostly inflammatory genes. TLRs recognize pathogen-associated molecular patterns (PAMPs) or endogenous inflammation-associated molecules [98–100]. TLRs recognize distinct molecular structures on microbes, and, in several cases (e.g., recognition of viruses by TLR3, TLR7, TLR8, and TLR9), different sets of TLRs have been associated with the response to different classes of microorganisms [101–103]. PAMPs are for diverse microbially derived molecules expressed predominantly on innate immune cells [104–106]. To date, in human 11 TLRs family members have been identified in the human [107–109]. Bacterial DNA is containing unmethylated CpG motifs which are able to act as important regulators of human neutrophil functions via TLR9. For example, stimulation of the TLR9 pathway via CpG oligonucleotides (ODN) induces CXCL8 production by neutrophils via the generation of peroxynitrite (ONOO-) [110, 111].
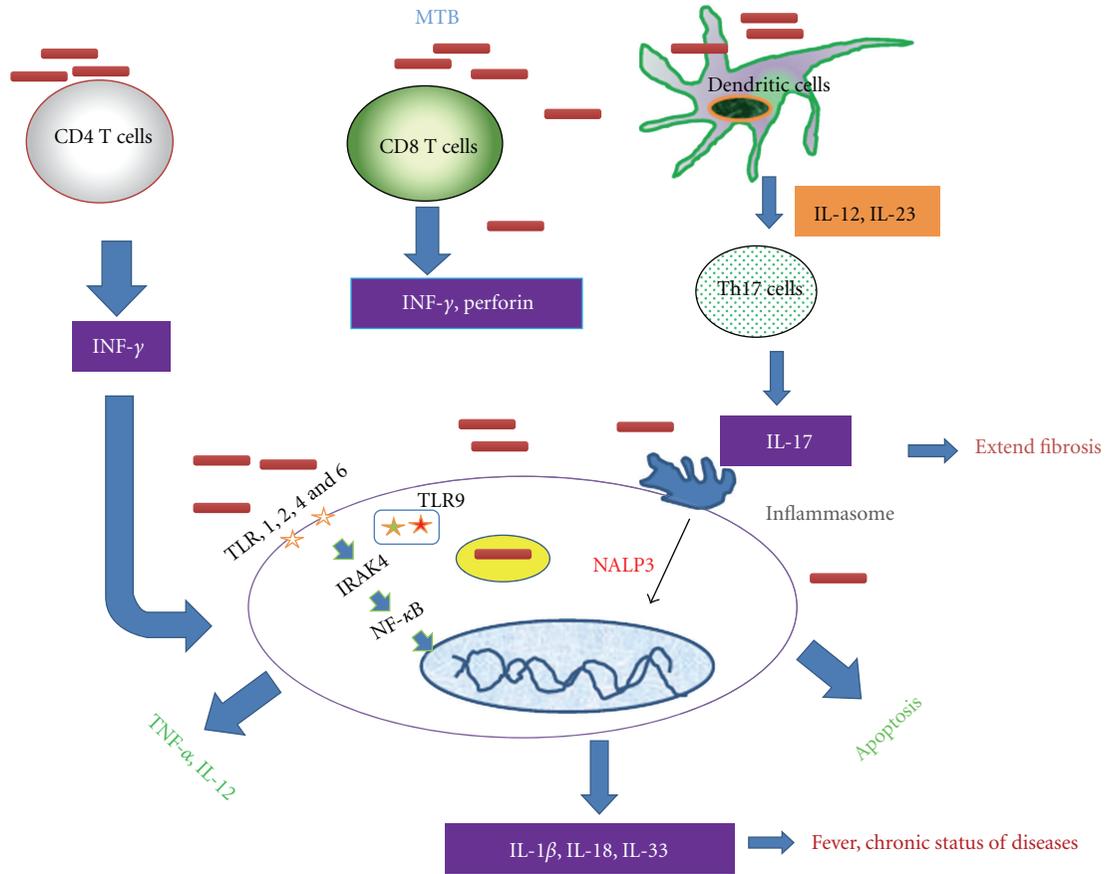
FIGURE 1: Schematic diagram of immunopathology of TB. After inhalation of MTB, the immune system cells (CD4, CD8, DCs, and Th17) were activated. By these T cells, Th1 cytokines were released. In next steps by involvements of released mediators especially IFN-γ, lungs macrophages were activated. After activation of macrophages by MTB or cytokines, inflammatory mediators such as IL-12 and TNF-α or inflammasome mediators such as IL-1β via TLRs or inflammsome signal transduction pathways were released. Besides of activation, macrophages underwent to the apoptosis processing which is described as a main host protection strategy against the TB infection. Abbreviations used are: MTB; mycobacterium tuberculosis, TLR; toll-like receptors.

Upon inhalation, MTB travels to the lung where it infects resident alveolar macrophages [112]. This initial infection leads to an innate immune response, which includes stimulation of TLRs that recognize pathogens and are located on the plasma membrane and within endosomes of host cells. Emerging of data indicated that MTB is specifically recognized by TLRs 2, 4, and 9 [113].

TLR activation upregulates transcription of proinflammatory cytokines IL-1β, TNF-α, and IL-6, which are essential for the recruitment of immune cells to the site of infection and controlling MTB infection [114, 115].

Mice deficient in the TLR/IL-1R family receptor adaptor molecule MyD88 have been shown to be highly susceptible to infection with MTB, which could be suggested to major role for this pathway in innate defense against the MTB [116, 117]. In this line it has been demonstrated that TB induces ROS in cells which accounts for the induction of proinflammatory cytokines [118].

Besides, it has been shown that TLR2-ROS signaling could play a crucial role in the expression of CXCL8 and CCL2 in human monocytes. In addition, both p38 and ERK1/2 activations are essential for 30-kDa Ag-stimulated CCL2 production by monocytes [119]. In correspondence, earlier studies by using human overexpressed TLR2 or TLR4 cell lines suggested that viable MTB could activate cells via both TLR2 and TLR4 pathways [120].

Recent studies in mice with inactivated TLR genes showed that TLR2 is important in controlling and surviving the MTB infection [121, 122]. However, some observations suggested that TLR4 is also important for survival of MTB infection [123–125]. However, other studies indicated that the importance of TLR4 may depend on the dose of MTB used for challenge [126] or the choice of mouse strain [127].

In this regard, human studies show that polymorphisms of TLR2 or TLR4 may result in increased susceptibility to microbial infections, possibly by changing the balance of Th1/Th2 response [128–132]. Interestingly, Fenhalls et al. reported that the expression of TLR in TB lung granulomas is related to the presence or absence of immunohistologically detectable IL-4 [133]. Now it became clear that changes

in TLR expression might represent useful markers of the immunological status of patients and their contacts. When examining the TLR distribution in TB granulomas lesions, it was shown that TLR1, TLR2, and TLR4 were expressed in both immune cells and nonimmune cells; however, TLR9 was detectable in immune cells [134]. In an animal model with TB, it has been shown that TLR8-deficient mice succumb rapidly to infection with *M. tuberculosis*, despite controlling efficiently the infection in different organs. Exaggerated mortality was due to massive liver necrosis and was reversed by in vivo treatment with Abs to IL-1 and TNF-α. Thus, TLR8 plays a key role in damping inflammation and tissue damage in *M. tuberculosis* infection [135].

3.2. Role of Inflammasomes Signaling in MTB. In addition to TLR recognition, a newly discovered class of intracellular danger-sensing proteins, the nucleotide-binding domain, leucine-rich repeats containing family proteins known as NLRs, sense pathogens and pathogen products in the cell cytoplasm [136]. With more than twenty members, the NLRs function in host protection against a broad range of danger signals. Several NLRs function in immunity through the formation of a multiprotein complex known as an inflammasome [137]. The importance of inflammasome signaling against MBT previously has been described. For example, it has shown that M. marinum, a mycobacterium that naturally infects fish and amphibians, activates IL-1β production in a NLRP3, and caspase-1-dependent manner in vitro, but no in vivo investigation was conducted [138]. Another report showed that M. bovis BCG, the vaccine strain of Mtb, can limit caspase-1 and IL-1β activation due to a putative protease Zmp1. In this latter study, however, there was no analysis of Pycard, Nlrp3 or Nlrc4, to directly implicate the inflammasome components [139]. Finally it has shown that MTB-infected THP-1 human monocyte cell line secretes IL-1β in a PYCARD and NLRP3-dependent process, but did not investigate the role of the inflammasome in vivo [140]. When activated by a specific danger signal, the inflammasome forms and results in recruitment and processing of pro-caspase-1, which in turn processes IL-1β and IL-18 to their active forms for secretion from macrophages. Although the host's innate immune response to MTB infection is critical for the initial defense against bacteria, the adaptive immune response is ultimately required for containment of the infection in the chronic stage of disease. Adaptive immunity to MTB infection is characterized by the appearance of antigen-specific CD4$^+$ T cells that secrete interferon gamma (IFN-γ), which is responsible for activating macrophages to kill intracellular bacteria [141]. CD8$^+$ T cells are also important for controlling bacteria during the chronic phase of MTB infection [142]. Chronic MTB infection is controlled by granuloma formation which contains, but does not eliminate bacteria [143]. IL-1β induces the release of GM-CSF which leads to the activation and increased survival of monocytes/macrophages and enhanced oxidative burst in the lungs; thus, maintaining and prolonging inflammatory reactions, IL-1β is secreted by activation of inflammasome signaling which is triggered by signal transduction via TLRs

and purinergic receptors. Apoptosis-associated speck-like protein, containing a caspase recruit domain (ASC) and pro-caspase 1, forms a multimeric cytosolic molecular complex known as the NALP3 proinflammatory cytokine regulation can be critical to long-term survival of Mtb infection. In vivo assessments of IL-1$\alpha/\beta^{-/-}$, IL-1R$^{-/-}$, and IL-18$^{-/-}$ mice have shown that these cytokines play a role in limiting bacterial lung burden, regulating other cytokines, nitric oxide production, and forming organized granulomas [144–146]. Recently it has been shown that caspase-1 independent IL-1β production is critical for host resistance to MTB and does not require TLR signaling in vivo. Besides they show that (although IL-1β induction by MTB in vitro depends on TLR triggering and the inflammasome for signals 1 and 2 respectively, both triggers are dispensable for IL-1β production in vivo in mice infected with the pathogen [147].

In this regard, recently it has been reported that here we show that MTB-induced IL-1β secretion in human and mouse macrophages in vitro, and this process was dependent on PYCARD, caspase-1, and NLRP3, but not NLCR4. In vivo, murine Pycard helps protect the host from death during chronic MTB infection while the effects of Casp-1 and NLP3 were negligible. The inability of Pycard$^{-/-}$ mice to form organized granulomas and the reduced presence of lung dendritic cells indicate a breakdown in host defense against MTB. Thus, we identify PYCARD as a critical protein involved in host response to MTB infection in an inflammasome-independent manner [148].

4. Conclusion and Future Research

TB is a chronic disease with protection strongly depending on mycobacterial containment. The mechanisms underlying this containment are highly complex comprising different T cell populations with their complex signaling. Although CD4 T cells, CD8 T cells, $\gamma\delta$ T cells, macrophages, and DCs are apparently important role in the pathogenesis of TB; however, the exact mechanisms of the TB and crosstalk between involved cells are not well described.

Although T cells are the major mediators of protection against the TB, effector functions are mostly provided by macrophages/DCs which is not much appreciated. The crosstalk between T cells and macrophages and DCs is achieved by various cytokines, notably IFN-γ, TNF-α, IL-17, and IL-1-β. This cross talk first results in APC activation, that is, the ability of APC to control MTB replication (Figure 1). Taken together, present literature suggests a role for novel signal transductions and molecules in pathogenesis of TB. Currently available animal models for TB could be employed to further address the role of new cells such as Th17, Treg, and their possible value as therapeutic target in the treatment of TB.

Abbreviations

AMP: Adenosine monophosphate
APC: Antigen-presenting cell
BAL: Bronchoalveolar

CCR: CC-chemokine receptor
cDC: Conventional dendritic cell
CD8$^-$ cDC: CD8$^-$ conventional dendritic cell
CD8$^+$ cDC: CD8$^+$ conventional dendritic cell
COPD: Chronic obstructive pulmonary disease
CXCL: CXC-chemokine ligand
CTL: Cytotoxic T lymphocytes
CMR: Cell-mediated reactions
CLR: C-type lectin receptors
DTH: Delayed-type hypersensitivity
DCs: Dendritic cells
IFN-γ: Interferon gamma
LPS: Lipopolysaccharide
LTα: Lymphotoxin α
MTB: Mycobacterium tuberculosis
MMPs: Matrix metalloproteinase
NK: Natural killer cells
NOS2: Nitric oxide synthase 2
ODN: Oligodeoxyribonucleotides
ONOO: Peroxynitrite
PRRs: Pattern recognition receptors
PAMPs: Pathogen-associated molecular patterns
pDC: Plasmacytoid dendritic cell
PMN: Polymorphonuclear cells
ROS: Reactive oxygen species
TLR: Toll-like receptor
TB: Tuberculosis.

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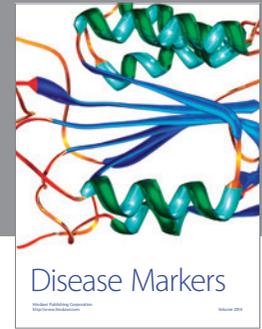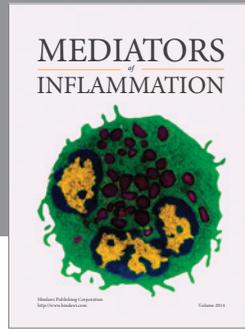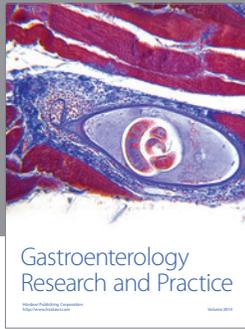
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