

Alveolar NLRP3 Inflammasome Regulators

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Mycobacterium tuberculosis, the causative agent of tuberculosis (TB), is a successful intracellular pathogen that is responsible for the highest mortality rate among diseases caused by bacterial infections. During early interaction with the host innate cells, *M. tuberculosis* cell surface antigens interact with Toll like receptor 4 (TLR4) to activate the nucleotide-binding domain, leucine-rich-repeat containing family, pyrin domain-containing 3 (NLRP3) canonical, and non-canonical inflammasome pathways. NLRP3 inflammasome activation in the alveoli has been reported to contribute to the early inflammatory response that is needed for an effective anti-TB response through production of pro-inflammatory cytokines, including those of the Interleukin 1 (IL1) family. However, overstimulation of the alveolar NLRP3 inflammasomes can induce excessive inflammation that is pathological to the host. Several studies have explored the use of medicinal plants and/or their active derivatives to inhibit excessive stimulation of the inflammasomes and its associated factors, thus reducing immunopathological response in the host. This review describes the molecular mechanism of the NLRP3 inflammasome activation in the alveoli during *M. tuberculosis* infection. Furthermore, the mechanisms of inflammasome inhibition using medicinal plant and their derivatives will also be explored, thus offering a novel perspective on the alternative control strategies of *M. tuberculosis*-induced immunopathology.

Keywords: NLRP3 inflammasomes ; alveolar macrophages ; pulmonary epithelial cells ; medicinal plants ; medicinal plant derivatives ; immunopathology ; interleukin 1 cytokines

1. Introduction

Several studies have shown the effectiveness of medicinal plants and their bioactive derivatives as a promising approach to TB treatment since these are naturally sourced compounds with minimal side effects ^{[1][2][3][4]}. Medicinal plants and their respective active compounds exhibit their anti-inflammatory mechanisms through inhibition of the NLRP3 inflammasome-associated transcripts ^{[5][6]}, inflammasome assembly ^{[7][8]} and production of inflammasome proteins, including IL1 cytokines ^[9] on in vitro and in vivo *M. tuberculosis* infection models. The current review reveals the molecular mechanism behind inflammasome activation on resident alveolar macrophages and pulmonary epithelial cells that results in IL1 cytokine production, which have been shown to contribute to the alveolar inflammatory response during *M. tuberculosis* infection. Furthermore, medicinal plants and their active derivatives that can be explored to prevent overstimulation of the alveolar NLRP3 inflammasome and their mechanisms of action will be reported as a novel host-directed therapy against *M. tuberculosis*.

2. *M. tuberculosis* Interaction with Alveolar Macrophages and Pulmonary Epithelial Cells

Previously, not much was known about specific receptors expressed by pulmonary epithelial cells during *M. tuberculosis* infection. Bermudez and Goodman ^[10] initially proposed that *M. tuberculosis* use microtubules and microfilament pathways to gain entry into pulmonary epithelial cells. This was shown by significant reduction of intracellular bacilli when these pathways were blocked ^[10]. Lee et al. ^[11] revealed an upregulation of Dectin-1 receptors in a TLR-2 dependent manner of A549 pulmonary epithelial cells during *M. tuberculosis* infection. Through the production of a Dectin-1 receptor protein, they showed that these non-phagocytic cells might use this receptor for recognition of *M. tuberculosis*. The *M. tuberculosis* strains of East-African Indian and Euro-American lineages both induced down-regulation of the NOD1 receptor of the A549 pulmonary epithelial cells at 72 h post-infection ^[12]. However, a time course analysis of the NOD-associated receptors is needed to establish their involvement in the recognition of *M. tuberculosis*. Mannose and DC-SIGN receptors have not been linked to *M. tuberculosis* invasion of pulmonary epithelial cells and this area remains to be investigated.

TLRs are involved in the recognition of different *M. tuberculosis* cell wall-associated structures, such as acylated lipoproteins (TLR1, TLR2, TLR6), ESAT-6, mycolic acid (TLR2), acylated lipomannan (TLR4), and trehalose dimycolates (TLR3, TLR4, and TLR9), respectively ^[13]. Sequeira et al. ^[14] showed the role of TLR2 of pulmonary epithelial cells in the

production of pro-inflammatory cytokines during infection by *M. tuberculosis*. Inhibition of TLR2-mediated response by mycolic acid and *mce1* operon mutant significantly reduce the production of both IL8 and MCP-1, which suggests that TLR2 is essential to effective inflammatory response of pulmonary epithelial cells to *M. tuberculosis*. Previously, we showed an increased expression of TLR2, TLR3, TLR5, and TLR8 in pulmonary epithelial cells at 48 h post-infection by genetically diverse *M. tuberculosis* clinical strains of East-Asian and Euro-American lineages, leading to production of a diverse range of inflammatory cytokines. Upregulation of TLR4 was only induced by the Beijing (East-Asian) and F11 (Euro-American) strains, while TLR1, TLR6, TLR7, and TLR9 were downregulated by all strains [15].

A transcriptomic study performed by Hadifa et al. [12] revealed an increased expression of TLR1 and TLR3 by East-African Indian and Euro-American lineages of *M. tuberculosis* at 72 h post-infection of A549 pulmonary epithelial cells. Furthermore, the East-African Indian strain induced increased expression of TLR2, TLR5, and TLR9; while the Euro-American strain induced down-regulation of TLR4, TLR5, and TLR9. Both transcriptomic studies [12][15] indicate the TLRs are activated by different lineages of *M. tuberculosis* in pulmonary epithelial cells at 48 and 72 h post infection and these PRRs may be the main receptors used by this pathogen to gain entry into these cells.

Upon stimulation of the alveolar macrophages and pulmonary epithelial cells TLRs by *M. tuberculosis* PAMPs, the MyD88, TIR-domain-containing adapter-inducing interferon- β (TRIF), TRIF-related adapter molecule (TRAM), Toll-interleukin 1 receptor domain containing adaptor protein (TIRAP), B-cell adaptor for PI3K (BCAP), and sterile alpha and TIR motif containing (SARM) are adaptor molecules that are central components of the TLR signalling pathway [16]. Previously, we showed that genetically diverse strains of *M. tuberculosis* induced high enrichment of the TLR signalling pathways in pulmonary epithelial cells with increased expression of the MyD88 adaptor molecule [17]. Several studies have linked phagocytosis of *M. tuberculosis* by alveolar macrophages to the MyD88-signalling pathway [18][19] with a highly impaired inflammatory response in MyD88-knockout studies [20][21]. Thus, the activation of these adaptor molecules in pulmonary epithelial cells and alveolar macrophages results in downstream signalling cascade, leading to the activation transcriptional factors that are responsible for expression of inflammatory cytokines, including interferons and IL1 cytokine family [22]. Moreover, interaction between *M. tuberculosis* surface antigens with TLR4 triggers the NF- κ B signalling pathway to induce expression of IL1 β and IL18, whose maturation and production is dependent on the inflammasome assembly [23].

3. Activation of the Alveolar NLRP3 Inflammasome during *M. tuberculosis* Infection

Inflammasome is a multi-protein complex intracellular structure, which induces maturation of inflammatory cytokines, IL1 β , and IL18 through the activation of caspase-1 and caspase-4/11 [24]. The activation of the inflammasome is triggered by signalling pathways that involves host PRRs, such as NOD-like receptors and TLRs [25]. Inflammasomes function in modulating host defence response, as well as pyroptosis, which is an inflammatory induced lytic mode of cell death that can be caspase-1 or caspase-11 dependent [26]. The assembly of an inflammasome is a coordinated signalling event, which is essential to producing an immune response after sensing *M. tuberculosis* [27][28]. The canonical NLRP3 inflammasomes is mediated by the activation of Caspase 1, while the non-canonical NLRP3 activation can be activated downstream of Caspase 4/11, respectively [25][22].

The second signal of the canonical inflammasome pathway involves the assembly of the NLRP3 inflammasome complex, which results in the recruitment of adaptor molecule, CARD and pro-caspase-1 in order to induce the processing and secretion of IL1 β and IL18 cytokines. Pulmonary epithelial cells exhibit increased regulation of NLRP3 (by only F11 and H37Rv strains) PYCARD (ASC) and CASP1 during early infection by clinical strains of *M. tuberculosis* [15]. This upregulation may be time and lineage specific since the Euro-American lineage downregulated CASP1 at 72 h [12] in pulmonary epithelial cells. High levels of the mature IL18 were predominantly observed in *M. tuberculosis*-stimulated pulmonary epithelial cells, which indicated the upregulation of IL18 expression at both transcriptional and post-transcriptional levels, suggesting the involvement of CASP1 enzymatic activity [29]. There were no significant differences in the production of IL1 β by pulmonary epithelial cells, which increased from 24, 48, and 72 h post-infection by wild type, *Mycobacterium tuberculosis* curli pili (MTP) mutant and complemented strains of *M. tuberculosis* [30], suggesting that IL1 cytokine production is not dependent on the MTP antigen. It should be noted that the activation of the canonical NLRP3 inflammasome pathway in pulmonary epithelial cells, if present, may be dependent on the lineage of the infecting strain, as well as the infection time as shown by the differences observed for the Euro-American and East-African Indian lineages [12][15]. Stimulation of the canonical inflammasome by *Mycobacterium* and its associated factors is well described and characterised in alveolar macrophages [28][31][32], as these cells have been shown to produce inflammatory IL1 β and IL18 [31][32][33].

Non-canonical NLRP3 inflammasome mediated by CASP4/11 [34] has been shown to be activated by intestinal Gram-negative bacterial such as *Citrobacter rodentium*, *Escherichia coli*, *Legionella pneumophila*, *Salmonella typhimurium*, and *Vibrio cholera* [22] and other parasites such as *Leishmania amazonensis* [35]. The pathogen's LPS and other surface antigens have been associated with non-canonical NLRP3 inflammasome activation through interaction with Guanylate binding proteins (GBPs). To our knowledge, there is no evidence of the non-canonical stimulation of the NLRP3 inflammasome by *M. tuberculosis* in pulmonary epithelial cells from transcriptomics and proteomics studies; and this area remains to be investigated. However, the NLRP3 CASP4/11-dependant inflammasome is activated in macrophages during *M. tuberculosis* infection [36]. Collectively, these studies indicate that *M. tuberculosis* stimulate alveolar macrophages canonical and non-canonical NLRP3 inflammasome, leading to production of inflammatory cytokines, IL-1 β , and IL18 in a TLR4-NF- κ B dependent manner. Furthermore, despite increased expression of the NLRP3 inflammasome transcripts and subsequent IL1 cytokine production in pulmonary epithelial cells, the presence of this complex and other types of inflammasomes such as NLRP6, NLRC4, and AIM2 remains to be investigated and confirmed in future studies. The activation of a canonical and non-canonical alveolar NLRP3 molecular mechanism during *M. tuberculosis* infection is depicted in **Figure 1**.

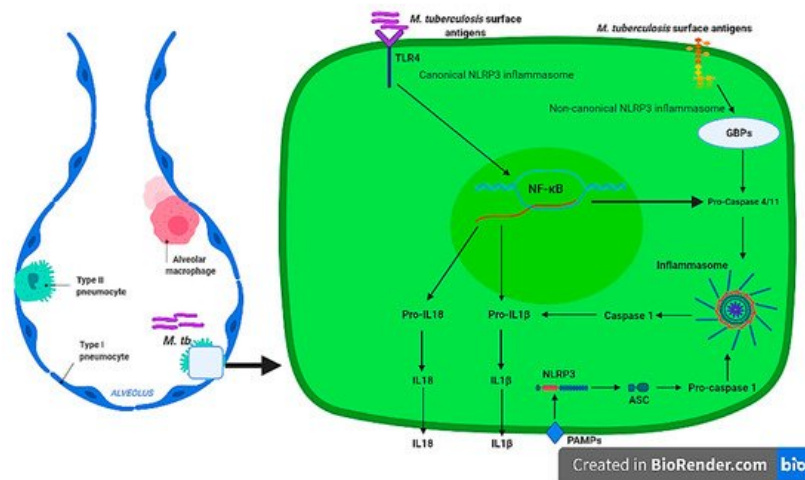


Figure 1. Overview of the alveolar NLRP3 inflammasome activation on alveolar innate cells during *M. tuberculosis* infection. The host PRRs (TLR4) is activated by *M. tuberculosis* surface PAMPs stimulate the NF- κ B transcriptional factor to transcribe *IL1*, *IL18*, and *CASP4/11* that are processed by activation of the inflammasome complex through NLRP3 and CASP1. Image was created in BioRender.com (accessed on 23 August 2021).

It is apparent that alveolar macrophages produce IL1 cytokines [28][29][30][36][37] through the activation of canonical and/or non-canonical NLRP3 inflammasome by the TLR-MYD88 signalling pathway, which results in stimulation of NF- κ B transcriptional factors that transcribe pro-inflammatory cytokines during *M. tuberculosis* infections. However, this mechanism remains to be confirmed for pulmonary epithelial cells. IL1 are among the group of pro-inflammatory cytokines that are essential in host defence against *M. tuberculosis* [31]. Mice with IL1 α and IL1 β double knockouts and IL1R type I-deficient mice display a defective granuloma phenotype accompanied with increased mycobacterial growth [33]. IL18 is known as an interferon- γ inducing factor, which has a vital role in T helper1 (Th1) response [38][39] and has been shown to be responsible for the production of pro-inflammatory cytokines, chemokines, and transcriptional factors [40][41]. Moreover, IL18 defective mice were shown to be highly susceptible to *M. tuberculosis* and BCG strains [42]. Despite the critical role played by IL1 cytokines of the NLRP3 inflammasome, overproduction of pro-inflammatory cytokines without efficient anti-inflammatory response has been associated with increase disease severity and high bacterial burden [43] that can compromise effective host response during TB infection. The presence of IL1 β was associated with caseous granulomatous inflammation during *M. tuberculosis*, while blocking IL1 β production relieved pulmonary inflammation [44]. Significantly high IL1 β and IL18 was identified in drug resistant compared to drug susceptible TB [45], while high cytokine concentrations were identified in patients with a severe disease [46]. Therefore, the ability of pulmonary epithelial cells and alveolar macrophages to produce IL1 (IL1 β and IL18) cytokines through the activation of the inflammasome may contribute to the inflammatory response during early infection by *M. tuberculosis* that is pathological to the host, thus novel strategies must be exploited to regulate this response.

4. Medicinal Plants and Their Bioactive Derivatives as Regulators of Alveolar NLRP3 Inflammasome during *M. tuberculosis* Infection

The high prevalence of TB worldwide is partly due to development of drug resistant strains, rendering the current treatment regimen ineffective [47][48][49]. Several studies have proposed the use of medicinal plants or their bioactive compounds with antimycobacterial activity [3][7][50][51][52][53]. However, recent studies have also exploited the use of medicinal plants and/or their derivatives that are regulators of the immune system during *M. tuberculosis* infection [54][55][56]. Medicinal plants and their respective bioactive compounds that regulate the components of the immune system may be a promising strategy in controlling Mycobacterial infections because they are not directly targeting the bacillus, reducing the pathogen's need to develop drug resistance and selective pressure [57]. Therefore, medicinal plants and their bioactive derivatives may provide a novel host-directed perspective in controlling immunopathology in the alveoli through inhibition of the NLRP3 inflammasomes pathways that are crucial in the production of IL1 β and IL18 cytokines during *M. tuberculosis* infections. Medicinal plants and/or their bioactive derivatives that are used to inhibit NLRP3 inflammasome gene transcription, formation of the inflammasome complex and production of NLRP3 inflammasome proteins (including IL1 cytokines) are reviewed below.

There are many medicinal plant bioactive derivatives that act as NLRP3 inflammasome transcript inhibitors identified in non-*M. tuberculosis* models. These include Arctigenin [58], Silymarin [59], Rutin [60], Genistein [61], Aloe emodin [62], Anemoside B4 [63], epigallocatechin-3-gallate [64], Resveratrol [65], Silibinin [66], Artemisinin [67], Icarin [68], Polydatin [69], Cinnamaldehyde [70], Huangkui capsule [71] whose administration results in the inhibition of the inflammasome-associated transcription on both in vitro and in vivo models (**Figure 2**). It is crucial that these medicinal plant compounds be tested in *M. tuberculosis* in vitro and in vivo models to identify their potential use as host-directed immunomodulatory plant derivatives that can be used to prevent lung pathology during infection.

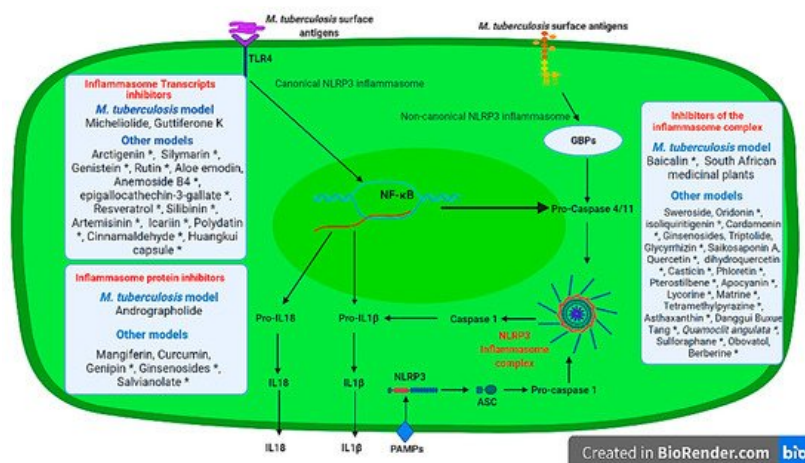


Figure 2. Medicinal plant and/or bioactive regulators of the NLRP3 inflammasome that can be exploited as immunomodulatory host-directed adjuvants during *M. tuberculosis* infection. Compounds denoted with * were tested in vivo. Image was created in BioRender.com (accessed on 23 August 2021).

Several in vitro and in vivo models have identified other medicinal plant derivatives that have been found to inhibit NLRP3 inflammasome proteins and subsequent IL1 production; and these include Ginsenosides (Retinoblastoma and Compound K) [72][73], Curcumin [74], Genipin [75], Mangiferin [76], Salvianolate [77] that were derived from *Panax ginseng*, *Curcuma longa*, *Gardenia jasminoides*, *Mangifera indica*, *Salvia miltiorrhiza* medicinal plants, respectively.

There is growing appreciation of medicinal plants and their bioactive molecules in management of inflammatory response regulated by the NLRP3 inflammasome as excellently reviewed by several authors [78][79][80][81]. To date, only five studies [5][6][7][8][9] have explored the use of medicinal plants and/or their bioactive derivatives in the management of the inflammasome in *M. tuberculosis* infection models. There is a growing understanding that *M. tuberculosis* infection is a multifaceted condition that is also driven by the host inflammatory response. Thus, controlling the alveolar NLRP3 inflammasome seem to be one of the novel strategies for host directed control measures of pathological response induced by *M. tuberculosis*.

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