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# Duality of lipid mediators in host response against *Mycobacterium tuberculosis*: good cop, bad cop

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## Abstract

Lipid mediators play an important role in infection- and tissue injury-driven inflammatory responses and in the subsequent inhibition and resolution of the response. Here, we discuss recent findings that substantiate how *Mycobacterium tuberculosis* promotes its survival in the host by dysregulation of lipid mediator balance. By inhibiting prostaglandin $E_2$ ($PGE_2$) and enhancing lipoxin production, *M. tuberculosis* induces necrotic death of the macrophage, an environment that favors its growth. These new findings provide opportunities for developing and repurposing therapeutics to modulate lipid mediator balance and enhance *M. tuberculosis* growth restriction.

## Introduction

The recent World Health Organization report on the worldwide incidence of tuberculosis (TB) indicates that in 2012 there were an estimated 8.6 million incident cases of TB and 1.3 million deaths [1]. In addition, it is estimated that one third of the world's population is latently infected with *Mycobacterium tuberculosis* (Mtb) and is at a 5-10% lifetime risk of reactivation, thereby fueling the cycle of transmission. Clearly, TB remains a global emergency. A significant impediment to TB treatment and global eradication of the disease is a 6-month multi-drug treatment regimen. Prolonging treatment reduces rates of relapse, but the extended period leads to non-compliance and the emergence of drug-resistant mutants. Additionally, despite successful treatment, relapses still occur in 5% of the patients because of bacterial persistence [2]. Furthermore, TB-HIV co-infected patients receiving anti-retroviral treatment and TB chemotherapy are at risk of developing immune reconstitution inflammatory syndrome [3,4]. Other major challenges to TB treatment and significant threats to global health are the worldwide increase in multi-drug-resistant (MDR) TB and the reported presence of extensively drug resistant TB in 92 countries [1]. In the last decade, therefore, a great deal of research effort in TB was invested in the discovery and development of new TB drugs that target the bacteria and in conducting clinical trials to evaluate their efficacy in shortening TB treatment regimens. However, there is high likelihood of also developing resistance against these newly discovered drugs.

Though still incomplete, our understanding of how Mtb evades the host response has advanced significantly. In addition, through the use of *in vivo* animal models, immune factors that restrict or promote Mtb growth have been identified. This commentary will focus on lipid mediators, since converging findings from several groups point to their significant role in regulating multiple pathways of host control of Mtb. We integrate these studies to highlight how lipid mediators form the central nexus influencing the various macrophage outcomes, including cell apoptosis, necrosis, and tumor necrosis factor (TNF) production, thereby positioning them as strong targets for host-directed therapy (HDT). HDTs have the potential to shorten TB treatment regimens with first-line TB drugs and, importantly, to improve treatment outcomes when used in conjunction

with second-line drugs for MDR patients. Another potential advantage of HDT is the ability to restrain inflammatory responses in the lung and thereby ameliorate pulmonary pathology. In this regard, treatment of Mtb-infected mice with ibuprofen alone was found to be sufficient to reduce the number and size of lung lesions [5], and a meta-analysis study of 41 clinical trials found that corticosteroids were effective in reducing mortality in patients with TB [6].

Eicosanoids are a family of bioactive lipid mediators derived from arachidonic acid (AA), which is released from membrane phospholipids by phospholipases. There are three major pathways that are involved in the production of eicosanoids: (i) the cyclooxygenase pathway (COX-1 and COX-2), which produces prostaglandins and thromboxanes; (ii) the lipooxygenase (LOX) pathway (5-LOX, 12-LOX, and 15-LOX), which catalyzes the production of leukotrienes and lipoxins; and (iii) the cytochrome p40 pathway, which generates hydroxyeicosatetraenoic acids and epoxyeicosatrienoic acids. In addition, omega-3 essential eicosapentaenoic acid (EPA) and docosahexaenoic acid are substrates for the production of resolvins, protectins, and maresins that are termed as specialized pro-resolving mediators (SPMs) [7–10]. Prostaglandins and leukotrienes are the initial mediators of the inflammatory response and stimulate recruitment of neutrophils and monocytes. Lipoxins and SPMs have anti-inflammatory pro-resolving activities and contribute to the resolution phase of an inflammatory response. Prostaglandin $E_2$ ($PGE_2$) and prostaglandin $D_2$ ($PGD_2$) function as pro-inflammatory mediators during the initial phase of an inflammatory response. However, later, through a process termed "lipid mediator class switching", these mediators reprogram exudate neutrophils to a pro-resolution phenotype by inducing 15-LOX and lipoxin generation [11]. Lipoxins are also double-edged mediators with anti-inflammatory and pro-resolving activities [12]. Ligation of the lipoxin $A_4$ ($LXA_4$) receptor on neutrophils arrests their migration but in monocytes signals for migration and non-phlogistic responses [13]. Thus, lipid mediators participate in the initiation and resolution of inflammation and aid in the return to homeostasis.

In this commentary, we will first present evidence that eicosanoids regulate host defense against Mtb. Based on fundamental findings, it is well established that TNF is critical to restricting Mtb growth [14] but that inhibition of apoptosis is a virulence strategy that Mtb employs to evade innate defense mechanisms of the host [15]. Furthermore, type I interferons (IFNs) have been shown to impinge on host-protective responses against TB [16]. We will then review the growing body of literature that mechanistically links these three host responses to regulation by lipid mediators. We conclude that these advances are paving the way for lipid mediator manipulation as promising targets for HDT in TB. However, one needs to be mindful of the possibility that these host-targeted therapeutic interventions for TB may have a deleterious effect on the control of coincident viral infections.

## *Mycobacterium tuberculosis* and lipid mediators

There is rapidly accumulating evidence that the eicosanoids leukotrienes, prostaglandins, and lipoxins are critical to determining the outcome of Mtb infection in the host. The first evidence that lipid mediators may serve as druggable host targets came from Mtb infection studies in mice deficient in 5-LOX (*Alox5*$^{-/-}$) [17], the enzyme required for both leukotriene and lipoxin biosynthesis. These mice had elevated expression of interleukin-12 (IL-12) and IFN$\gamma$, and exhibited significantly lower Mtb burdens in their lungs at 5 weeks following infection, compared with wild-type (WT) mice [17]. The further finding that administration of a lipoxin analog to Mtb-infected *Alox5*$^{-/-}$ mice reversed the protection [17] indicates that lipoxins, and not leukotrienes, negatively regulate host control of Mtb. In contrast, other studies have reported that inhibition of 5-LOX with the pharmacological inhibitor MK886 abrogated host control of experimental pulmonary TB and that this was associated with a reduction in leukotrienes [18,19]. Despite the discrepant outcomes between *Alox-5*$^{-/-}$ and MK886-treated mice, the finding that ALOX-5 variants are associated with susceptibility to TB supports that 5-LOX products, lipoxin and leukotrienes, regulate host-protective immune response against Mtb [20].

## Tumor necrosis factor and lipid mediators

Findings from a forward genetic screen in zebrafish larvae found that mutations in the *Ita4h* locus encoding leukotriene A4 hydrolase (LTA4H) conferred hypersusceptibility to *Mycobacterium marinum* infection [21]. LTA4H catalyzes the conversion of leukotriene $A_4$ to the pro-inflammatory eicosanoid, leukotriene $B_4$ ($LTB_4$). The study found that the phenotype of the mutant was not due to the lack of $LTB_4$ but rather to the deviation of the eicosanoid substrates toward the production of anti-inflammatory lipoxins [21]. The increased levels of lipoxin inhibited TNF production and resulted in increased growth of mycobacteria. Contrary to expectation, modulation of LTA4H expression with anti-sense RNA and morpholinos showed that not only LTA4H-low but also LTA4H-high zebrafish exhibited increased bacterial growth [22]. LTA4H-low animals expressed high levels of $LXA_4$ and low levels of TNF. LTA4H-high animals, on the other hand, expressed enhanced levels

of $LTB_4$, increased TNF, and an overall heightened inflammatory state [22]. Additional experimental manipulations of TNF levels in the fish revealed TNF to be the key executioner of increased necrosis and bacterial growth in both states of LTA4H expression [22]. Together, these studies indicate that a fine balance of the eicosanoid mediators is essential to generate the right level of TNF since either too little or too much of the cytokine can be detrimental to host control of Mtb. The finding that optimal TNF levels and control of mycobacterial growth can be achieved by modulation of lipoxin levels with pharmacologic modulators [22] or via overexpression of an enzyme that inactivates $LTB_4$ [23] underscores the potential of targeting lipid mediators for the development of HDTs.

Subsequent work on the LTA4H promoter showed that a functional single-nucleotide polymorphism influenced the level of transcription in macrophages, thereby providing an explanation for why adjunctive therapy with dexamethasone benefitted only a subset of patients with TB meningitis [24]. Reanalysis of study patients for LTA4H polymorphism showed that patients who benefitted from dexamethasone adjunctive treatment had a high LTA4H-expressing genotype but that those who did not benefit had the low-LTA4H-expressing genotype [22]. This finding is paradigm-shifting and indicates that TB treatment with HDT may have to take into consideration the individual's genotype.

## Apoptosis and lipid mediators

Modulation of the macrophage cell death pathway is exploited by Mtb as a virulence strategy to survive in the host [25]. Early studies clearly delineated two distinct outcomes following infection of alveolar macrophages with virulent and avirulent Mtb strains. Infection of murine bone marrow-derived macrophages [26] or human monocyte-derived macrophages [27] with avirulent Mtb strains resulted in TNF-dependent apoptosis of the infected cell while virulent Mtb evaded this innate defense mechanism and instead induced macrophage necrosis as the major mode of cell death. Mechanistically, virulent Mtb, via annexin-1 blockade, prevents the complete formation of the apoptotic envelope [28] and inhibits apoptosis induction. Apoptosis is host-protective since it restricts Mtb growth [29,30], enhances antigen presentation by dendritic cells, and induces an early Mtb-specific adaptive Th1 response [31,32]. On the other hand, necrosis results from an irreversible increase in the mitochondrial permeability transition, resulting in mitochondrial damage and enhanced release of cytochrome *c* [33]. Together, these studies underscore the pivotal role for the necrotic form of macrophage cell death in creating a safe niche for virulent Mtb.

In subsequent studies, the mechanistic basis for the induction of disparate cell death pathways by avirulent and virulent strains of Mtb was found to be at the level of lipid mediators. Avirulent Mtb induced $PGE_2$ production which protected against cellular necrosis by preventing mitochondrial inner membrane damage [34] and by promoting rapid plasma membrane repair [35]. On the other hand, $LXA_4$ was the dominant lipid mediator produced by macrophages infected with virulent Mtb and was responsible for induction of necrosis. $LXA_4$ suppressed COX-2 expression and synthesis of $PGE_2$, thereby deviating the infected macrophage toward a necrotic fate [34]. The ensuing findings that prostaglandin E synthase (*Ptges*)-deficient mice [34] and mice lacking the prostaglandin receptor EP2 [36] have increased susceptibility to Mtb infection [36] provide strong evidence that $PGE_2$ and the apoptotic death of macrophages are critical to regulating Mtb growth *in vivo* [34].

In this commentary, the role of apoptosis in Mtb infection is discussed under the rubric of lipid mediators and in this context the literature supports apoptosis as being host-protective. However, we would like to emphasize that the role of apoptosis in Mtb infection is contentious and that several studies have reported that the induction of apoptosis is indeed a virulence strategy of Mtb [37–41]. Clearly, additional extensive studies with Mtb clinical isolates are necessary to determine how the two forms of cell death regulate Mtb growth and pathogenesis *in vivo*.

## Type I interferon and lipid mediators

Several studies have shown that type I IFNs promote Mtb growth. For example, clinical isolates of the Beijing family induce a strong type I IFN response, and *in vivo* studies have shown that type I IFNs exacerbate disease in Mtb-infected mice [42,43]. Enhancing type I IFN expression in the lungs of WT mice through intranasal poly-IC administration [44] or exposure to influenza A virus [45] also resulted in increased pathology and bacterial load in the lungs in comparison with control mice. Consistent with IFN's deleterious effect on the host, IFN$\alpha$ receptor knockout mice (IFNARKO) mice were found to be more resistant to Mtb infection compared with their WT counterparts [46,47], and poly-IC treatment had no effect on IFNARKO mice [44]. Removal of TPL2, a negative regulator of type I IFN, also led to excess type 1 IFN and exacerbated disease in Mtb-infected mice [48]. Type I IFN downregulates the host immune response by inhibiting the production of IL-1$\beta$ [49,50], a cytokine critical to protection against Mtb infection [51–54]. Type I IFN also inhibits IL-12 production and IFN$\gamma$-mediated killing by macrophages [55]. Findings from a seminal study performed in a cohort of TB patients from London and South Africa showed that active disease

was associated with a type I IFN gene signature and that the intensity of the signature correlated with severity of disease [56]. Subsequently, a similar disease-related type I IFN gene signature was reported in South African and Gambian cohorts [57] and in an Indonesian cohort [58].

Despite the growing evidence of the cross-talk between IL-1β and type I IFN and the importance of IL-1β to host protection, the mechanism of how IL-1β promotes resistance remained unclear. In a recent study, Mayer-Barber and colleagues [59] probed this question by first examining the typically studied mediators of protection, including IFNγ, nitric oxide synthase 2 (NOS2), IL-12p40, and TNF, and found that these were not abrogated in the susceptible IL-1R1KO mice. Instead, the authors discovered differential expression levels of eicosanoid mediators between WT and IL-1RKO mice [59]. In comparison with bronchoalveolar lavage fluid of WT mice, that of IL-1R1KO mice had significant reductions in $PGE_2$ and $PGF_{2a}$ and concomitant increases in the levels of $LXA_4$ and $LTB_4$. Using a number of elegant *in vitro* and *in vivo* approaches to ablate COX-2 and $PGE_2$ expression, the authors were able to effectively demonstrate that, during Mtb infection, IL-1β induces COX-2 expression which in turn upregulates $PGE_2$ and subsequent Mtb growth restriction. IFNARKO mice that are resistant to Mtb express significantly high levels of IL-1β and $PGE_2$ [59]. Furthermore, removal of IFNAR1 in IL-1R1KO mice reduced their susceptibility compared with IL-1R1KO alone, clearly indicating that type I IFN abrogates host protection [59]. This study definitely shows that the suppression of type 1 IFN by IL-1β-induced $PGE_2$ is a key step in conferring resistance to Mtb. Importantly, the authors were able to confirm their observations in two human cohorts where they found that patients with a lower $PGE_2$-to-$LXA_4$ ratio had worse sputum grade [59]. Mice lacking IL-1α and IL-1β express high type 1 IFN levels [59]. Treatment of these mice with zileuton, a US Food and Drug Administration-approved 5-LOX inhibitor, together with $PGE_2$ led to decreased lung pathology and bacterial burden [59], indicating that lipid mediators are attractive host targets for therapeutic intervention in TB.

## Summary and closing remarks

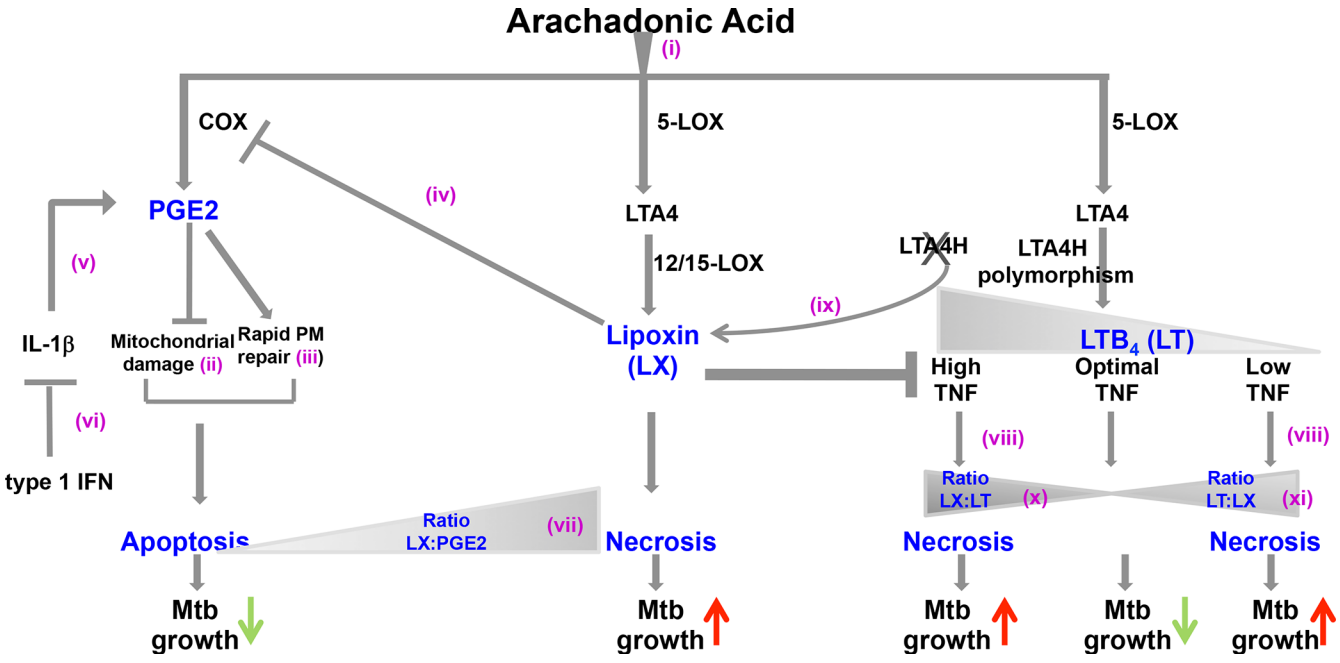
In Figure 1, we summarize the findings that demonstrate the contribution of the three major eicosanoid pathways to the ability of the host to restrict Mtb. AA metabolism leads to the induction of $PGE_2$, lipoxin, and leukotrienes (i). $PGE_2$ promotes apoptosis and prevents necrosis by inhibiting mitochondrial damage (ii) and inducing rapid plasma membrane repair (iii). However, lipoxin can inhibit $PGE_2$ via inhibition of COX-2 expression (iv) and ablate the protective effect of $PGE_2$ in the macrophage, leading to necrosis. IL-1β enhances $PGE_2$ expression (v), but IL-1β expression is inhibited by type I IFN (vi). Thus, in the presence of type I IFN, IL-1β expression is abrogated and consequently $PGE_2$ levels decrease. This results in an overall increased ratio of lipoxin to $PGE_2$ in the host, promoting Mtb growth (vii). LTA4H induces leukotriene which in turn upregulates TNF expression. Low expression of LT4AH leads to reduced TNF (viii) and inability to control bacteria and subsequent necrosis of macrophages. The fact that removal of LTA4H deviates eicosanoid expression toward enhanced lipoxin levels (ix) indicates that an increased ratio of lipoxin to leukotrienes leads to macrophage necrosis (x). High expression of LTA4H is also detrimental since it tips the balance toward high leukotriene expression, excess TNF and macrophage necrosis (xi), and enhanced growth of Mtb. This indicates that the levels of lipoxin and leukotriene should be in equilibrium for optimal macrophage response to Mtb.

Together, the findings demonstrate that striking the proper balance between the levels of lipoxin, $PGE_2$, and leukotrienes is critical for successful control of Mtb. Thus, several drug targets in the eicosanoid pathway can be exploited to modulate the expression of the individual eicosanoids to the right level.

The paradigm that $PGE_2$-mediated acquisition of the apoptotic phenotype by macrophages is host-beneficial is not without caveats. For example, lipid bodies contained in foamy macrophages promote the intracellular survival of mycobacteria [60,61] but are also intracellular sites for $PGE_2$ generation [61]. Also, contrary to expectation, mice treated with ibuprofen, a drug that suppresses $PGE_2$ production, exhibit reduced bacterial load [5]. Of note, this study used the C3HeB/FeJ strain of mice that develop necrotic lung pathology similar to active TB. Clearly, further mechanistic studies are required to determine how ibuprofen treatment and decreased $PGE_2$ can be beneficial in the context of extensive lung pathology. Also, *in vivo* studies need to examine whether ibuprofen and other non-steroidal anti-inflammatory drugs protect the host against TB by mechanisms that are independent of host lipid mediators.

To understand the role of lipid mediators during influenza infection, lipidomic profiling was performed in mice infected with a low-pathogenicity influenza strain (X31/H3N2) and a high-pathogenicity strain (PR8/H1N1). Comparison of lipid class composition showed that 12/15-LOX mediators were associated with the resolution phase of the X31 infection but that a high percentage of pro-inflammatory 5-LOX mediators

**Figure 1. Cross-regulation of the eicosanoid pathways in restricting Mtb growth**




Abbreviations: COX, cyclooxygenase; IFN, interferon; IL-1β, interleukin-1-beta; LOX, lipooxygenase; LTA4, leukotriene A4; LTA4H, leukotriene A4 hydrolase; $LTB_4$, leukotriene $B_4$; Mtb, *Mycobacterium tuberculosis*; $PGE_2$, prostaglandin $E_2$; PM, plasma membrane; TNF, tumor necrosis factor.

correlated with the H1N1 strain [60]. These data suggest that a similar analysis of the composition of lipid mediators induced by different clinical strains of Mtb may yield important data regarding the temporal role of lipid mediators in regulating pulmonary pathogenesis and inform whether the infecting strain of Mtb may have to be considered in HDTs.

As clinical trials with HDTs are implemented, it is important to consider the duality in function of several of the lipid mediators. There is strong evidence that high lipoxin levels abrogate control of Mtb growth. However, lipoxin also reduces airway inflammation [61] and therefore it would be important to investigate whether HDT targeting the lipoxin pathway may have adverse effects of enhanced immunopathology. In this regard, it is worth investigating whether pro-resolving mediators that have no anti-inflammatory effects will provide a new therapeutic opportunity for complete resolution of lung pathology in patients with TB. It may also be important to study the effect of lipoxin on non-hematopoietic cells since it induces bactericidal/permeability-increasing protein in human mucosal epithelia [62]. A recent study reported that influenza virus A uses the $PGE_2$ pathway to enhance its replication in the host [63]. The virus limits the induction of type I IFN and also inhibits cell apoptosis by upregulating the expression of $PGE_2$. Inhibition of $PGE_2$ via genetic or pharmacological means enhanced the ability of the host to control viral replication. This finding suggests that $PGE_2$ that is protective in Mtb infection has an opposing role in influenza virus infection and raises a note of caution regarding lipid mediator-directed HDT against Mtb. Conversely, it is equally important to consider whether inhibition of $PGE_2$ as an HDT against influenza virus infection may lead to a burst in type I IFN and be detrimental if a co-infection with Mtb is present.

Despite these caveats, the exciting findings on how the balance of lipid mediators dictates the ability of macrophages to control Mtb growth will open up novel pathways for developing HDTs. Targeted delivery of the HDTs can be employed to ameliorate effects on viral co-infections.

## Abbreviations

AA, arachidonic acid; COX, cyclooxygenase; HDT, host-directed therapy; IFN, interferon; IFNARKO, interferon alpha receptor knockout mice; IL, interleukin; LOX, lipooxygenase; LTA4H, leukotriene A4 hydrolase; $LTB_4$, leukotriene $B_4$; $LXA_4$, lipoxin $A_4$; MDR, multi-drug-resistant; Mtb, *Mycobacterium tuberculosis*; $PGE_2$, prostaglandin $E_2$; SPM, specialized pro-resolving mediator; TB, tuberculosis; TNF, tumor necrosis factor; WT, wild-type.

## Disclosures

The authors declare that they have no disclosures.

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