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Too much of a good thing: How modulating LTB_4 actions restore host defense in homeostasis or disease

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Abstract

The ability to regulate inflammatory pathways and host defense mechanisms is critical for maintaining homeostasis and responding to infections and tissue injury. While unbalanced inflammation is detrimental to the host; inadequate inflammation might not provide effective signals required to eliminate pathogens. On the other hand, aberrant inflammation could result in organ damage and impair host defense. The lipid mediator leukotriene B_4 (LTB_4) is a potent neutrophil chemoattractant and recently, its role as a dominant molecule that amplifies many arms of phagocyte antimicrobial effector function has been unveiled. However, excessive LTB_4 production contributes to disease severity in chronic inflammatory diseases such as diabetes and arthritis, which could potentially be involved in poor host defense in these groups of patients. In this review we discuss the cellular and molecular programs elicited during LTB_4 production and actions on innate immunity host defense mechanisms as well as potential therapeutic strategies to improve host defense.

Keywords

Leukotriene B_4; innate immunity; inflammation; host defense; immune regulation; microbicidal activity

1. Introduction

The ability of innate immune cells to properly recognize, respond, and eliminate invading pathogens is a requisite for host survival. Microbial infections quickly elicit an inflammatory program that induces the recruitment of phagocytes, such as macrophages, monocytes and neutrophils. These newly migrated cells further enhance the production of pro-inflammatory

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mediators such as cytokines, chemokines, growth factors, and bioactive lipids in the inflammatory milieu. After exposure to pathogens, sentinel cells such as epithelial cells and phagocytes (tissue resident macrophages and dendritic cells) detect pathogen associated molecular patterns (PAMPs) via binding to pattern recognition receptors (PRRs). Activation of PRRs such as Toll like receptors (TLRs) trigger the signaling programs that culminate in the generation of inflammatory cytokines and lipid mediators to provide signals essential to the recruitment of cells involved in the control of pathogens. The bioactive lipid mediator leukotriene B_4 (LTB_4) is produced primarily by neutrophils and macrophages and signals through its high or low affinity receptor B leukotriene receptor (BLT) 1 or 2, respectively, to enhance phagocyte antimicrobial effector functions. However, aberrant levels of LTB_4 can be detrimental to host response and may be pathogenic in inflammatory diseases.

Effective inflammatory programs induced during infections can be compromised by underlying health conditions [1]. Although inflammation is important for coordinating immune responses during infection, excessive inflammatory responses can be destructive. Patients with chronic inflammatory diseases, such as diabetes, arthritis, and atherosclerosis have dysregulated inflammatory response functions and are more prone to infections [2–4].

This review covers the current understanding of the role of LTB_4 and BLT1 on host defense mechanisms and how modulating the LTB_4/BLT1 pathway can be therapeutically targeted to respectively amplify or inhibit host defense in settings of immunodeficiency or aberrant inflammation.

2. LT synthesis and receptors

2.1 LT synthesis

LTs are part of a large family of lipids termed eicosanoids that are derived from the Greek word “eicosa” since eicosanoids are made of 20 carbon atoms called eicosatetraenoïc acid. The synthesis of LTs involves several rate-limiting steps that comprise activation of phospholipase A_2 (PLA_2) and arachidonic acid (AA) release from phospholipids in the cellular membranes. Activation of 5-LO in concert with the 5-LO activation protein (FLAP) metabolizes AA to LTA_4, which is converted to LTB_4 by LTA_4 hydrolase. LTA_4 could alternatively be modified with glutathione by LTC_4 synthase to form LTC_4. Further modifications of LTC_4 give rise to LTD_4 and LTE_4. Since LTC_4, D_4, and E_4 contain a cysteine, they are known as the cysteinyl leukotrienes (CysLTs). Even though CysLTs exert stimulatory effects on macrophages and neutrophils, this review will focus primarily on LTB_4 actions. The main cellular sources of LTB_4 in both murine and humans are granulocytes, monocytes, and macrophages (Table 1) [5]. However, murine (RAW264.7 and J774) and human (THP1 and U937) macrophage cell lines express low levels of 5-LO and produce barely detectable levels of LTB_4 [6]. Non-immune cells are also capable to produce LTB_4. Some cell types have been reported to express some but not all of the LT-synthesis enzymes, which renders these cells incapable of synthesizing leukotrienes independently. However, these cells may be able to contribute to the synthesis of LTs in a process known as transcellular biosynthesis [7]. An example of transcellular biosynthesis of LTB_4 is between neutrophils-erythrocytes, and keratinocytes and endothelial cells [8–12]. Table 1 lists the

cellular expression of leukotriene synthesis enzymes. Although this topic is of interest, a more comprehensive review can be found at [13].

5-LO activity is dependent on various signals including calcium release and phosphorylation, which control the catalytic site and the translocation of 5-LO within the cell. In a resting cell, 5-LO location varies depending on the cell type [14]. In neutrophils and peritoneal macrophages, 5-LO is located in the cytosol whereas in alveolar macrophages and Langerhans cells, 5-LO is located within in the nucleus [15–17]. Upon cell activation, increased intracellular calcium levels induce 5-LO to translocate to the perinuclear or plasmatic membrane where it can metabolize AA into LTA_4 [18]. 5-LO activity is triggered by various stimuli such as pathogens, cytokines, and immune complexes [19]. During infection, pathogens have limited abilities to increase intracellular calcium levels and therefore are poor 5-LO activators alone. However, treating infected cells with a calcium ionophore or opsonized zymosan particles are able to greatly enhance LT synthesis [20, 21]. Table 2 lists the relative levels of LTB_4 produced in response to various stimuli. The molecular mechanisms that regulate 5-lipoxygenase activation are reviewed here [22, 23].

2.2 LTB_4 receptors

There are two G protein coupled receptors (GPCRs) for LTB_4, BLT1 and BLT2. BLT1 is a high-affinity receptor and BLT2 is a low-affinity receptor. Since other fatty acid metabolites besides LTB_4 are able to activate BLT2, the effects of BLT2 signaling are not limited strictly to LTB_4 effects [24]. Distribution of BLT1 and BLT2 on cells and tissues vary between mouse and human [24]. On human cells, BLT1 expression is limited to leukocytes (Table 1) and BLT2 is ubiquitously found on many cell types. On mouse cells, BLT1 expression is detected on leukocytes and BLT2 is found on intestinal epithelium and keratinocytes [24, 25]. BLT1 can be coupled to Gαi or Gαq that culminate to decrease cyclic AMP (cAMP) levels and increase intracellular calcium levels, respectively [26]. We have previously shown that BLT1 utilizes mainly Gαi to enhance antimicrobial effector functions in alveolar macrophages [26]. Figure 1 demonstrates a schematic of LTB_4/BLT1-induced effector functions in innate immune cells. The low affinity receptor BLT2 is also expressed in phagocytes, but its role in host defense is poorly studied. Previously, we have shown blocking BLT2 does not influence phagocytosis and bacterial killing in alveolar macrophages [27]. However, BLT2 might be a relevant receptor for other antimicrobial effector functions in different organs [24]. Recently, Zhang and Brown have shown that in the absence of BLT1, BLT2 enhances macrophage *Borrelia burgdorferi* phagocytosis. It remains to be determined whether BLT2 amplifies neutrophil chemotaxis to the site of infection and whether BLT2 controls antimicrobial peptide production in the skin or in the gut. However, BLT2 regulation and actions are out of the scope of this review.

3. Effects of LTB_4 on host defense mechanisms

3.1 Migration and chemotaxis

Neutrophils are the first cells recruited to the site of infection or injury. There are various steps involved in successful recruitment of neutrophils: rolling, adhesion, and transendothelial migration [28]. LTB_4 is well known for its role as a neutrophil

chemoattractant from distant sites to the site of inflammation [29–31]. Also, LTB_4 participates with chemokine gradients to further enhance neutrophil chemotaxis towards other chemoattractants such as fMLP, C5a, and heme [32–34]. Neutrophils from mice lacking BLT1 are not able to swarm and cluster to a focal damage site. $BLT1^{-/-}$ neutrophils have smaller neutrophil clusters than wild type neutrophils [35], demonstrating the importance of LTB_4/BLT1 signaling in neutrophil accumulation. Additionally, neutrophil recruitment is not unidirectional. Reverse transendothelial migration has been reported where neutrophils reenter the blood stream after migration to the site of infection or injury [36]. In a model of ischemia-reperfusion injury, LTB_4 and neutrophil elastase compose an important axis that drives reverse transendothelial migration. Neutrophils that reenter the vasculature are able to migrate to secondary organs and have the potential to cause injury [37].

3.2 Phagocytosis

We, and others, have shown that LTB_4/BLT1 signaling amplifies the actions of different signaling components required for ingestion of particles. The first demonstration that LTB_4 enhances phagocytosis was shown by Wirth et al using a model of *Trypanosoma cruzi* infection [38]. After this, Dr. Peters-Golden's group pioneered in demonstrating the role of endogenous LTs in amplifying phagocytosis of antibody-opsonized targets [39, 40]. Both genetic and pharmacologic blockage of LTB_4/BLT1 actions greatly reduces ingestion of a myriad of pathogens, including both gram-positive bacteria (*Streptococcus pneumoniae*) [27], gram-negative bacteria (*Klebsiella pneumoniae* [41]), fungi (*Histoplasma capsulatum* [42, 43], *Candida albicans* [44], and *Paracoccidioides braziliensis* [45]), and parasites (*Leishmania braziliensis* [46], *L. amazonensis* [47], and *T. cruzi* [38, 48]).

In addition to this extensive list of pathogens, the molecular mechanisms involved in LTB_4-mediated amplification of phagocytosis have been studied. BLT1 signaling enhances activation of Syk, a protein tyrosine kinase, important for Fcγ R-mediated phagocytosis [26, 49]. When macrophages are challenged with IgG-opsonized targets, LTB_4 enhances phagocytosis of IgG-RBC in an Fcγ R1-dependent manner. This enhancement is attributed to the association of BLT1 with lipid raft formation and heightened signaling capabilities [50]. Furthermore, LTB_4 amplifies phagocytosis by increasing phosphorylation of kinases involved in the formation of a phagocytic cup, such as PKC-α, PKC-δ, PI3K, and ERK1/2 [51, 52]. However, the hierarchical role of these kinases in amplifying phagocytosis remains to be determined. Molecular studies regarding the signaling programs involved in the phagocytosis of nonopsonized pathogens are scarcer than opsonized targets. It has been shown that LTB_4 enhances *C. albicans* phagocytosis via activation of GαI-mediated PKC-δ and PI3K activation culminating in F-actin polymerization [53]. LT enhancement of yeast phagocytosis involves the activation of PKC and PI3K, with subsequent activation of LIM Kinase, decreased cofilin-1 activation, and ultimately, F-actin assembly [53]. Furthermore, LTB_4 enhances phagocytosis of fungi by increasing the expression of dectin-1, a main phagocytic receptor detecting fungal pathogens [42]. LTB_4-mediated dectin-1 expression is dependent on GM-CSF production and activation of the transcription factor PU.1 [44].

3.3 Pathogen killing mechanisms

We, and others, have extensively shown that LTB_4 is a potent neutrophil activator [41, 54–56]. 5-$LO^{-/-}$ neutrophils or neutrophils treated with leukotriene synthesis inhibitors have significantly lower ingestion of serum-opsonized *K. pneumoniae* [41]. Exogenous LTB_4 treatment restores phagocytic capabilities in 5-LO deficient neutrophils [40, 45]. After phagocytosis, neutrophils kill pathogens by producing toxic components within granules that are released in a process known as neutrophil degranulation [57]. When human neutrophils are infected *in vitro* with the parasite *L. amazonensis*, endogenous and exogenous LTB_4 promotes neutrophil degranulation [47]. Also, LTB_4 induces release of myeloperoxidase [55] and elastase in neutrophils [37, 58]. LTB_4 treatment of mice infected with influenza virus induced production of antimicrobial peptides β-defensin 3 and Cramp [59], the mouse ortholog of human cathelicidin LL-37. In human neutrophils, LTB_4 induces the production of LL-37 in a dose-dependent manner [56].

Reactive oxygen and nitrogen species (ROS and RNS) production is another important antimicrobial effector function that phagocytes use to kill pathogens. LTB_4 enhances the production of NADPH oxidase-dependent ROS generation [54, 60]. We, and others, have shown that LTB_4 enhances ROS-dependent NADPH oxidase activation via phosphorylation of the cytosolic subunit p47phox. This activation is dependent on PKC-δ [54], ERK-1/2 and PI3K activation [61]. LTB_4 is part of a positive-feedback loop in human neutrophils infected with *L. amazonensis*, which is important to kill parasites [47]. Similar to neutrophils, macrophages produce a variety of different microbicidal molecules such as ROS, RNS, antimicrobial peptides, and indoleamine deoxygenase (IDO). LTB_4 is known to enhance the generation of most microbidicidal molecules mentioned above. LTB_4-mediated ROS production in macrophages is dependent on PKC-δ-mediated p47phox and p40phox phosphorylation and membrane translocation in alveolar macrophages challenged with opsonized *K. pneumoniae* [52]. Furthermore, we also showed that aerosolized LTB_4 increases p47phox expression and membrane translocation during *Streptococcus pneumoniae* lung infection [62]. Additionally, our unpublished results show that macrophages from $BLT1^{-/-}$ mice have impaired phagocytosis and killing of gram-positive methicillin-resistant *Staphylococcus aureus* (MRSA), which correlates with diminished ROS production in macrophages from the BLT1 deficient mice.

LTB_4-dependent RNS production is dependent on NFκB and STAT1 activation [46]. LTB_4 treatment further enhances the production of nitric oxide (NO) in murine macrophages, which improves killing of different pathogens such as *L. amazonensis* and *T. cruzi* [52, 63]. It remains to be determined whether LTB_4 enhances noncanonical microbicidal effectors in macrophages such as antimicrobial peptides, tryptophan depletion (via IDO activation), GTPases, and transferrin receptor activation.

3.4 PRR activation and cytokine generation

TLRs are known to detect both PAMPs and danger associated molecular patterns (DAMPs). There are 11 TLRs in human and 13 in mouse. TLRs can be found on the cell surface of immune cells or in endosomes located within cells. The role of LTB_4 in TLR activation has been suggested [64–66]. TLR signaling induces pro-inflammatory cytokine responses [67,

68]. TLR2 is a cell surface receptor that senses peptidoglycan molecules commonly found on gram-positive bacteria and TLR9 is an endosomal receptor that detects DNA [67, 68]. LTB_4 stimulation upregulates the expression of TLR2 and TLR9 in human neutrophils [69]. Enhanced expression of TLRs could allow for neutrophils to better sense various pathogens and induce a stronger signaling cascade, which allows for a more potent immune response. Furthermore, LTB_4 is also known to amplify the actions of different PRRs. TLR activation is dependent on different adaptors such as myeloid differentiation factor 88 (MyD88) and TIR-domain-containing adapter-inducing interferon-β (TRIF). Most TLRs except TLR3 utilize MyD88, and only TLR3 and TLR4 utilize TRIF. MyD88 activation is followed by phosphorylation of downstream components such as IRAKs and TAK-1. LTB_4 enhances MyD88 expression and MyD88-dependent activation of NFκB, which are able to intensify the signaling potential of TLRs and other PPRs [64]. The mechanisms involved in LTB_4-enhanced MyD88 expression relies on enhancing the activation of STAT1, the main transcription factor responsible for MyD88 expression [70]. BLT1 activation leads to mRNA degradation of suppressor of cytokine signaling 1 (SOCS1), the major STAT1 negative regulator, which contributes to enhanced MyD88 expression and subsequent enhancement of TLR-mediated macrophage activation [64]. Furthermore, it has been shown that LTB_4 amplifies the phosphorylation of IRAK and TAK-1 in human neutrophils [66]. In all circumstances, through TLR and PRR activation, LTB_4 amplifies the induction of cytokine production. LTB_4/BLT1 enhancement of inflammatory cytokine production has been extensively studied. LTB_4 is known to induce the cytokines GM-CSF, TNF-α, IL-6 and IL-1β and the chemokines KC, MCP-1, CXCL1, and CXCL2 that are thought to enhance inflammatory responses [71, 72].

Another layer of immune regulation induced by LTB_4 is the expression of microRNAs (small ~22 nucleotides in length) that inhibits mRNA degradation or translation. We have shown that 5-LO deficient macrophages exhibit a decreased expression of a specific set of inflammatory microRNAs (inflammatory regulon). Among these microRNAs, we detected decreased levels of miR-155, miR-125b, and miR-146b in LT-deficient cells [73]. We have shown that these microRNAs specifically bind to *SOCS1* 3′UTR, restrict SOCS1 expression and enhance MyD88 expression [64]. Therefore, LTB_4/BLT1 axis provides very potent and pleiotropic signals by decreasing microRNA expression and allowing inflammatory programs to be elicited in macrophages.

4. Aberrant LTB_4 is detrimental to host defense

Chronic inflammatory morbidities are accompanied by aberrant LTB_4 production that is thought to negatively influence disease pathogenesis. Among the diseases that LTB_4 plays a detrimental role include type 1 and type 2 diabetes, arthritis, and atherosclerosis [74–80]. The bad reputation of LTB_4 comes from its capacity to maintain inflammatory programs in monocytes/macrophages and prolonging neutrophil recruitment to the inflammatory foci. LTB_4/BLT1 blockade is expected to dampen inflammatory responses and restore tissue homeostasis during chronic inflammation.

Besides increased production of LTB_4, chronic inflammatory diseases are often associated with co-morbidities, including the major threat of increased susceptibility to infections.

Although LTB_4 plays a beneficial role in promoting pathogen clearance, the counterintuitive effect of LTB_4 in chronic inflammatory diseases could be explained by the overwhelming inflammatory response and lack of proper phagocyte response to pathogens. Abundant LTB_4 production and detrimental host defense responses have been associated in a zebrafish model of *Mycobacterium marinum* infection. The authors showed that LTA_4 hydrolase (LTA_4H), the enzyme that converts LTA_4 to LTB_4, is an important susceptibility factor involved in Mycobacterium infection. Zebrafish expressing hyperactive LTA4H are hypersusceptible to *M. marinum* infection [81]. Additionally, overexpression of LTA4H produces high levels of LTB_4 that drive aberrant TNFα production and uncontrolled mycobacterial infections [82]. Furthermore, zebrafish expressing the enzyme that inactivates LTB_4, leukotriene B_4 dehydrogenase/prostaglandin reductase 1 (LTB4DH/PTGR1), exhibit lower bacterial numbers than WT zebrafish. The susceptibility to infection of LTB4DH mutant animals can be reversed with BLT1 antagonism, further implicating LTB_4 as detrimental to host defense during Mycobacteria infection in zebrafish [83].

Exaggerated LTB_4 is also detrimental to systemic infection (sepsis). 5-$LO^{-/-}$ mice or pharmacological inhibition of BLT1 actions protect mice during cecum ligation and puncture (CLP). 5-$LO^{-/-}$ and WT mice treated with a LT synthesis inhibitor have drastically lower levels of neutrophil infiltrates and lower levels of inflammatory cytokines such as IL-1β [84]. During CLP-induced sepsis, treatment with the BLT1 antagonist U-75302 decreases lung injury [85] as evidenced by decreased neutrophil recruitment. Therapeutically regulating 5-LO products or blocking BLT1 during or after sepsis may help prevent organ injury. Aberrant LTB_4 production also renders diabetic mice more susceptible to sepsis than nondiabetic animals. We have shown that increased LTB_4 drives MyD88 expression and mediates chronic systemic inflammation in diabetic mice. Diabetic $BLT1^{-/-}$ mice are protected from sepsis, which correlates with lower inflammatory cytokine production and decreased MyD88 expression.

Given the pleiotropic effects of LTB4 on amplifying the actions of immune receptors by influencing intracellular programs and gene transcription in macrophage and neutrophil activation [86], exaggerated LTB4 levels could be influencing both the actions of PRR (via increased expression of MyD88 [64, 73]), cytokine (GMCSF,TNF-a and IL1b [44, 64, 87]), and phagocytic receptors (FcRs and dectin receptor [50, 52]) and transcription factors (NFkB, AP1 and PU.1 [44, 64, 73]) to elicit inflammatory programs and cause organ injury and poor host defense.

The mechanisms involved in aberrant LTB4 production and poor systemic and localized host defense remains to be determined. However, preliminary data from our laboratory suggest that local uncontrolled LTB4 production drives a robust production of chemokines and cytokines along with overwhelming neutrophil migration to the site of infection that releases inflammatory mediators that cause tissue damage. Furthermore, exaggerated BLT1 activation seems to impair clearance of dead cells by controlling the expression of don’t eat me signals, such as CD47 [88]. When apoptotic cells are not cleared properly, these cells become necrotic and secrets many danger associated molecular patterns (DAMPs) [89, 90]. DAMP secretion might lead to LTB4 production which could be part of an amplification loop involved in chronic inflammation and lack of bacterial clearance observed in diabetes.

Whether these molecular events are involved in enhanced susceptibility to skin infections in people with diabetes remains to be determined and are an active research program in our laboratory.

5. Manipulating LTB_4 levels/actions as a therapeutic potential to control host defense

5.1 Enhance LTB_4 effects

There are many potential advantages to using LTB_4 in immunotherapeutic protocols, which include: (i) generation of proteins is relatively expensive, time consuming and subject to contamination with products of the vectors used to generate the protein, while lipids can be produced quickly and with a high degree of purity; (ii) because lipids exhibit are known to have a short half-life, it offers flexibility and precision in controlling localized or systemic actions; (iii) LTB_4 is safe to be administered to the human lung *in vivo*; and (iv) LTB_4 could amplify initial antimicrobial responses by enhancing pathogen recognition and phagocytosis, release of NADPH oxidase-derived ROS, and pro-inflammatory responses through MyD88 expression and activation of inflammatory transcription factors.

Treatment protocols employing exogenous LTB_4 can be greatly beneficial to patients known to exhibit attenuated LT synthesis such as in malnutrition [91], cigarette smoking [92], vitamin D deficiency [93], HIV infection [94], and bone marrow transplantation [95]. These patients are more susceptible to infection. Therefore, adding back LTB_4 to immunodeficient patients could potentially restore phagocyte response and favor appropriate host defense.

We, and others, have starting paving the way to establish treatment protocols to determine the therapeutic effects of LTB_4 in host defense. Exogenous LTB_4 treatment is able to boost effector functions in wild type mice. In a model of *Streptococcus pneumoniae* lung infections, aerosolized LTB_4 treatment was effective in restoring host defense mechanisms in 5-$LO^{-/-}$ mice and enhancing effector functions in wild type mice [62]. Intravenous injection of LTB_4 in macaques enhances plasma levels of the antimicrobial peptide α-defensins. Plasma from the treated macaques can neutralize pathogens *ex vivo* [96]. LTB_4 treatment during influenza virus infection reduces viral titers compared to untreated mice [59]. The reduction in viral titers correlates with enhanced levels of the cathelicidin-related antimicrobial peptide (Cramp). Neutrophils are a major source of Cramp so when mice are depleted of neutrophils, exogenous LTB_4 treatment during influenza infection is unable to control viral load [59].

A potential pitfall is the fact that LTB_4 could lead to overwhelming recruitment of neutrophils, which may contribute to tissue injury. Also, the stability and safety of LTB_4 *in vivo* is a concern, but its been shown that bronchoscopy instillation of LTB_4 into the airways of normal human subjects elicited a marked influx of neutrophils. Its inhalation proved to be well tolerated and caused no adverse effects on blood pressure, pulmonary function, or bronchial responsiveness [97].

The importance of LTB_4 during infections is clear and exogenous treatment with LTB_4 may be a potential therapeutic strategy. However, high LTB_4 levels during some infections or in

chronic inflammatory diseases may need to be blunted to limit inflammation and alternative therapeutic strategies to prevent infection-mediated organ injury are necessary.

5.2 Preventing exaggerated LTB_4 actions in host defense

Overwhelming production of inflammatory mediators and reactive oxygen species are known to be detrimental to host defense in different models of infection [98–101]. Therapeutic strategies to block the actions of inflammatory mediators could also restore protective host defense. In our laboratory, we are focusing our efforts in understanding whether preventing BLT1 and/or BLT2 actions could be an important tool to control exaggerated inflammatory response and poor host defense in people with preexisting chronic inflammatory conditions, such as diabetes, obesity, asthma, rheumatoid arthritis and elderly. It is known that people with diabetes are more susceptible to numerous infections, including systemic, respiratory, and skin infections [2–4]. Indeed, both innate and adaptive immune cells from diabetics have impaired functions including poor phagocytosis and killing of pathogens [102, 103]. We have shown that macrophages from diabetic mice produce higher levels of LTB_4 than from control mice even under basal conditions [65]. Although seemingly counterintuitive, the mechanism by which people with diabetes are more susceptible to infections may operate in a similar manner to other infections where high levels of LTB_4 is detrimental to host defense [81, 83]. We detected higher levels of LTB_4 in the serum of septic and diabetic mice when compared to the levels of LTB_4 detected in septic and nondiabetic mice. Diabetic mice treated with the 5-LO inhibitor AA-861 greatly improve survival during sepsis. The increase in survival correlates with reduction in IL-1β [65]. Since LTB_4 is able to enhance IL-1β levels through inflammasome activation [104] and that LTB_4/BLT1 signaling enhances MyD88 and NFκB activities [64], it is possible that LTB_4 synthesis inhibition or actions prevents overwhelming Toll-interleukin receptors, such as IL1R, IL18R1 and TLR actions prevents organ damage. Therefore, a potential therapeutic opportunity to treat sepsis in diabetic mice could rely on preventing overwhelming inflammation with a BLT1 antagonist along with antibiotics to prevent bacterial growth.

Our unpublished data also show the detrimental role of aberrant LTB_4 on host defense in diabetic mice in a model of local infection. Diabetic mice are more susceptible to MRSA skin infection than nondiabetic mice. Diabetic mice infected with MRSA have increased LTB_4 production in the skin, which correlates with uncontrolled production of inflammatory mediators and neutrophil migration. Topical treatment with a BLT1 antagonist improves skin host defense in diabetic mice, as evidenced by decreased lesion size and bacterial numbers (data not shown).

6. Conclusion

LTB_4 is a homeostatic determinant for optimal host defense in healthy individuals by driving pleiotropic actions on phagocytes that include phagocyte chemotaxis, amplifying macrophage/neutrophil antimicrobial effector functions, and production of cytokines. However, during chronic diseases characterized by aberrant LTB_4 levels, excessive LTB_4 could be responsible for impaired host defense mechanisms. In the era of antibiotic-resistant pathogens, new therapeutic strategies are critically needed. Modulating levels of LTB_4 to

either enhance or limit immune responses as appropriate is a potential strategy that could be used as a single agent or in combination with antibiotics for an added benefit. There is a great need of further research in areas of inflammation regulation under homeostatic conditions and during infections as well as understanding how chronic illnesses alter these immune responses. This will allow for the development of customized immunomodulatory therapies.

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Abbreviations

LT	leukotriene
PAMP	pathogen associated molecular patterns
PRR	pattern recognition receptor
AA	arachidonic acid
LO	lipoxygenase
cPLA$_2$	cytosolic phospholipase A$_2$
FLAP	5-lipoxygenase-activating protein
cysLT	cysteinyl LT
BLT	B leukotriene receptor
cAMP	cyclic adenosine monophosphate
PKC	protein kinase C
ERK	extracellular signal-related kinase
PI3K	phosphoinositide 3-kinase
NFκB	nuclear factor kappa B
AP1	activator protein 1

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Highlights

- LTB_4 triggers signaling programs necessary for effective clearance of pathogens
- LTB_4/BLT1 signaling enhances innate and adaptive immune receptor effector functions
- LTB_4 can therapeutically boost host defense in settings of host vulnerability
- Aberrant LTB_4 levels observed in chronic inflammation is harmful to host defense
- LTB_4 synthesis/actions blockage restores host defense in chronic inflammatory diseases

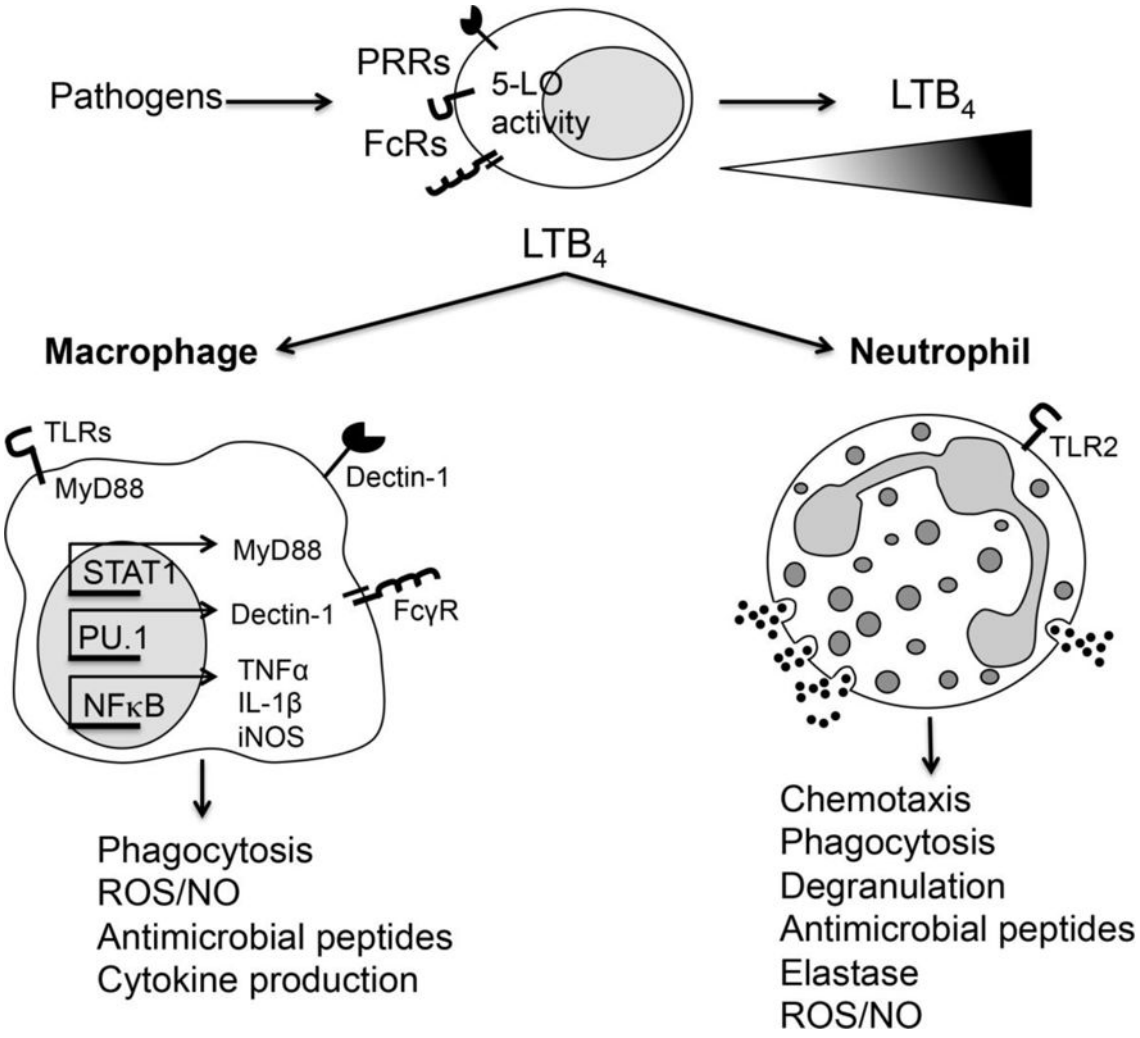

Fig. 1. Host defense mechanisms enhanced by LTB_4/BLT1 axis during microbial infection

Upper panel. Upon infection, microbial recognition triggers 5-LO activation to generate LTB_4 in phagocytes. *Lower panel*. LTB_4 amplifies macrophage and neutrophil effector function by enhancing the actions of different PRRs and FcR.

Table 1

Expression of LT synthesis enzymes and LTB_4 receptors in immune and structural cells.

Cell type	5-LO	FLAP	LTA_4 hydrolase	LTC_4 synthase	BLT1	BLT2
Neutrophil	+++	+	+++	−/+	+	+
Monocyte/macrophage	++	+	+++	+	+	+
Dendritic cell	+	+	++	+	+	+
Mast cell	+	+	+	++	+	+
Eosinophil	+	+	+	++	+	+
Endothelial cell	−	−	+	+	+	+
Red blood cell	−	−	+	−	−	−
Keratinocyte	−/+	−	+	+	+	+

Table 2

LTB_4 generation in response to various stimuli. ND not determined.

Cell type	Cytokines/Growth factors	Bacteria	Opsonized pathogen	Fungi	Viral
Neutrophil	++	++	+++	++	++
Monocyte/macrophage	++	++	+++	++	++
Dendritic cell	+	++	ND	+	+
Mast cell	+	+	ND	+	+
Endothelial cell	±	±	±	±	±