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## Leukotrienes: Underappreciated Mediators of Innate Immune Responses

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## BRIEF REVIEWS

Leukotrienes: Underappreciated Mediators of Innate Immune Responses<sup>1</sup>Marc Peters-Golden,<sup>2\*</sup> Claudio Canetti,<sup>\*</sup> Peter Mancuso,<sup>†</sup> and Michael J. Coffey<sup>\*</sup>

*Leukotrienes are bronchoconstrictor and vasoactive lipid mediators that are targets in the treatment of asthma. Although they are increasingly recognized to exert broad proinflammatory effects, their role in innate immune responses is less well appreciated. These molecules are indeed synthesized by resident and recruited leukocytes during infection. Acting via cell surface G protein-coupled receptors and subsequent intracellular signaling events, they enhance leukocyte accumulation, phagocyte capacity for microbial ingestion and killing, and generation of other proinflammatory mediators. Interestingly, a variety of acquired states of immunodeficiency, such as HIV infection and malnutrition, are characterized by a relative deficiency of leukotriene synthesis. The data reviewed herein point to leukotrienes as underappreciated yet highly relevant mediators of innate immunity. The Journal of Immunology, 2004, 173: 589–594.*

**B**ecause myeloid cells contain substantial amounts of esterified arachidonic acid (AA)<sup>3</sup> and constitutively express all of the enzymes necessary to hydrolyze it and metabolize it via the 5-lipoxygenase (5-LO) pathway, they are capable of generating large quantities of products termed leukotrienes (LTs) within seconds to minutes of encountering an activating stimulus. LTs are best known as bronchoconstrictor and vasoactive mediators released by Ag-triggered mast cells that contribute to asthmatic responses (1). However, because they are produced by all myeloid cell lineages in response to a panoply of stimuli, their broader participation in a wide array of pathologic inflammatory and acquired immune responses is increasingly recognized (2, 3). Much less well appreciated is their role in innate immune responses, the homeostatic function for which inflammation evolved. As molecules that can be generated in response to microbial stimuli and that mediate a variety of antimicrobial functions, LTs are ideally suited for such a role. Moreover, a variety of conditions associated with increased susceptibility to infection are characterized by a relative deficiency of LT synthesis. This article will review the body of evidence implicating LTs as key host-derived mediators of antimicrobial defense.

*LT synthesis, receptors, and signaling mechanisms*

Among the family of phospholipase A<sub>2</sub> enzymes capable of liberating AA from membrane phospholipids, cytosolic phospholipase A<sub>2</sub> (cPLA<sub>2</sub>) is considered the most important for providing substrate for LT biosynthesis (4). The free fatty acid is then oxygenated at C-5 by 5-LO in concert with the AA-binding protein, 5-LO-activating protein (FLAP), to generate the epoxide intermediate LTA<sub>4</sub>. Of note, activation of both cPLA<sub>2</sub> and 5-LO enzymes involves increases in intracellular calcium and is further enhanced by activation of certain protein kinases (5). LTA<sub>4</sub> is then hydrolyzed by LTA<sub>4</sub> hydrolase to LTB<sub>4</sub> or conjugated with reduced glutathione by LTC<sub>4</sub> synthase to form LTC<sub>4</sub>. LTB<sub>4</sub> is best known as a leukocyte chemoattractant and activator, and LTC<sub>4</sub> is the parent compound of the cysteinyl LTs (cysLTs), which also include LTD<sub>4</sub> and LTE<sub>4</sub>, and which account for the myotropic activity previously identified as slow-reacting substance (of anaphylaxis) and are important in the pathogenesis of asthma. Importantly, cell specificity exists in the profile of LTs generated, with mast cells and eosinophils synthesizing primarily cysLTs, neutrophils and dendritic cells synthesizing primarily LTB<sub>4</sub>, and macrophages producing a balance of both classes of LTs (see Table I).

The biological actions of LTs are mediated via ligation of G protein-coupled receptors (3, 6). In brief, LTB<sub>4</sub> and members of the cysLT family each interact with two distinct receptors, termed BLT1/2 and cysLT1/2, respectively. Most of the recognized actions of LTs appear to proceed through BLT1 and cysLT1. These are G<sub>q</sub>- and G<sub>i</sub>-coupled receptors that modulate downstream signaling pathways involving phospholipase C/intracellular Ca<sup>2+</sup>/protein kinase C, adenylyl cyclase, MAPK, PI3K, Rac, and NF-κB. Virtually all of the actions of LTs relative to antimicrobial defense are expected to follow from such signal transduction events. Key steps in LT biosynthesis and actions are illustrated in Fig. 1.

*LT production during innate immune responses*

Activation of LT synthesis during infection with bacteria, fungi, viruses, and protozoa has been observed in vivo in patients and animal models and in vitro in isolated leukocytes. For example, elevated levels of LTs have been reported in lung lavage fluid of

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<sup>3</sup> Abbreviations used in this paper: AA, arachidonic acid; LO, lipoxygenase; LT, leukotriene; cPLA<sub>2</sub>, cytosolic phospholipase A<sub>2</sub>; FLAP, 5-LO-activating protein; cysLT, cysteinyl LT; BLT, B leukotriene; PAMP, pathogen-associated molecular pattern; CR, complement receptor.

Table I. *Synthesis and Actions of LTs in Phagocytes*

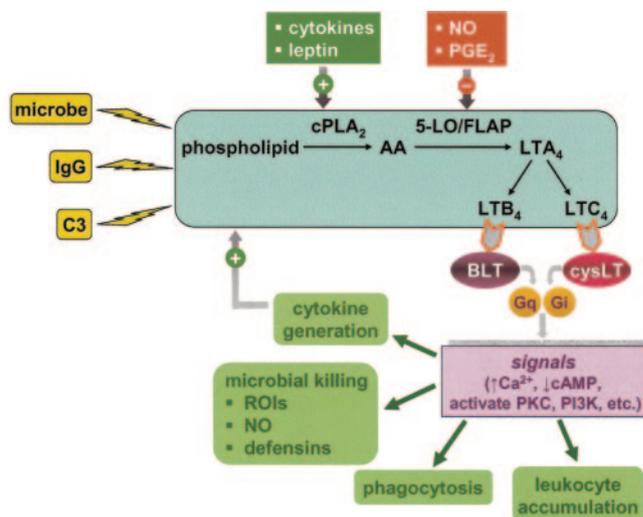
	cysLT	LTB <sub>4</sub>
Synthesis		
Macrophage	■	■
Neutrophil		■
Actions		
Macrophage		
FcR-mediated phagocytosis	■	■
Microbial killing	■	■
Cytokine generation	■	■
Neutrophil		
Recruitment/survival		■
FcR- and CR-mediated phagocytosis		■
Microbial killing		■
Cytokine generation		■

patients with bacterial (7) and respiratory syncytial viral (8) pneumonia, peripheral blood of patients infected with *Vibrio cholerae* (9), gastric fluid of patients infected with *Helicobacter pylori* (10), and nasal secretions of patients with rhinovirus (11). In vitro LT generation has likewise been observed in response to bacteria (12, 13), Mycobacterial species (14), *Toxoplasma gondii* (15), *Pneumocystis carinii* (16), *Histoplasma capsulatum* (17), influenza (18), and EBV (19). Although microbial activation of LT biosynthesis has been most extensively investigated in phagocytes, it has also been described in mast cells (20) and eosinophils (21).

The capacity of microbes to stimulate LT generation can best be understood by considering the molecules through which they interact with leukocytes and the effects of receptor ligation on requisite signal transduction pathways. Leukocytes interact with microorganisms through cell surface receptors for either opsonin molecules or intrinsic pathogen-associated molecular patterns (PAMPs).

The best-studied opsonins are IgG and complement. Interaction of IgG-opsonized microbes with phagocyte Fc $\gamma$  receptors triggers AA release and LT synthesis (12, 13), and this is to be expected in view of the well-documented capacity of Fc $\gamma$  ligation to increase intracellular calcium and activate a myriad of kinases (22). By contrast, ingestion of targets opsonized by complement peptides C3b and C3bi via complement receptor (CR) 1, CR3, and CR4 fails to trigger AA release or LT synthesis, yet can enhance AA release in response to other stimuli (23).

Ligation of pattern recognition receptors by PAMPs activates intracellular signaling cascades that culminate in the induction of NF- $\kappa$ B-dependent genes and the synthesis of inflammatory mediators, such as TNF- $\alpha$  and NO, that participate in antimicrobial defense. Zymosan, a carbohydrate component of yeast cell wall, is well known to trigger increases in intracellular calcium, release of AA, and LT biosynthesis (24–26). This substance is a ligand for multiple receptors, and both the mannose receptor (27) and TLR2 (28) may mediate LT synthesis. Gram-negative LPS are important PAMPs which signal via TLR4. The effects of LPS on LT biosynthesis are complex. Because LPS/TLR4 signaling does not result in increases in intracellular calcium (26), it is not sufficient to trigger LT synthesis. However, brief exposure of leukocytes to LPS can prime them for enhanced LT synthesis in response to an activating stimulus (29). Prolonged exposure of leukocytes to LPS, however, impairs their capacity for LT synthesis in response to activating stimuli, as a consequence of generation of inhibitory substances such as NO (30–32) (see below) and PGE<sub>2</sub> (31).



**FIGURE 1.** Synthesis and antimicrobial mechanisms of action of LTs. Microbes as well as opsonins IgG and C can trigger release of AA from membrane phospholipids and its metabolism to LTs. Neutrophils produce primarily LTB<sub>4</sub> and macrophages produce both classes of LTs. The expression and catalytic activity of these biosynthetic enzymes are influenced by relevant exogenous factors, with cytokines and leptin generally augmenting (indicated by “+”) and NO and PGE<sub>2</sub> generally inhibiting (indicated by “–”) LT production. By ligating BLT1/2 and cysLT1/2, LTB<sub>4</sub> and cysLTs activate Gq and Gi proteins to generate increased intracellular Ca<sup>2+</sup> and decreased cAMP, respectively; subsequent signal transduction events include activation of a number of downstream protein kinases. Resultant functional responses include recruitment of circulating leukocytes as well as activation of both recruited and resident leukocytes to ingest and kill microbes. Generation of cytokines serves to further amplify LT production and actions. PKC, Protein kinase C; ROIs, reactive oxygen intermediates.

#### *Antimicrobial effector functions of LTs*

An in vivo role for LTs in antimicrobial defense was first suggested by Demitsu et al. (33), who showed that i.p. administration of LTB<sub>4</sub> facilitated resolution of experimental bacterial peritonitis. An important role for endogenous LTs in host defense was first demonstrated by Bailie et al. (34), who reported that 5-LO-deficient mice exhibited impaired survival and pulmonary bacterial clearance in a model of *K. pneumoniae* pneumonia. Subsequent studies have documented a protective function of endogenous LTs in animal models including bacterial peritonitis (20), fungal pneumonia (35), and viral CNS infection (36). The effector functions involved in innate immune responses that are influenced by LTs include direct effects on leukocyte accumulation as well as their capacity for microbial phagocytosis and killing and indirect effects mediated by elaboration of other inflammatory molecules. Table I summarizes the relevant effects of both cysLTs and LTB<sub>4</sub> in both macrophages and neutrophils, and antimicrobial actions are further illustrated in Fig. 1.

**Leukocyte accumulation.** LTs induce leukocyte recruitment to an inflammatory site both by stimulating chemotaxis and by promoting firm adhesion to endothelial cells. LTB<sub>4</sub> has long been known to induce neutrophil migration in vivo and in vitro (37), and is now recognized to participate in the in vivo trafficking of CD4 and CD8 T lymphocytes (38). cysLTs participate in dendritic cell trafficking to sites of Ag stimulation (39) as well as to lymph nodes (40). The ability of cysLTs to promote microvascular leak (41) may contribute to neutrophil recruitment to sites of inflammation (42). In addition to their ability

to increase leukocyte recruitment, LTs also contribute to leukocyte accumulation in tissues by enhancing their survival via inhibition of apoptosis (43, 44).

**Phagocytosis.** Wirth and Kierszenbaum first noted the capacity of exogenous LTB<sub>4</sub> (45) and LTC<sub>4</sub> (46) to enhance macrophage phagocytosis of *T. cruzii* in 1985. Increased phagocytosis of IgG-opsonized bacteria has also been observed for macrophages in response to both classes of LTs (12), and for neutrophils in response to LTB<sub>4</sub> (47). An important role for specific endogenous 5-LO products in Fcγ-mediated phagocytosis was established in these studies by the use of 5-LO null mice, 5-LO and FLAP inhibitors, and specific receptor antagonists (see Table I). CR-mediated phagocytosis in neutrophils was also augmented by LTB<sub>4</sub> (47). It seems highly likely that the ability of LTs to enhance phagocytosis reflects the fact that the requisite signal transduction events downstream from opsonin or microbial recognition receptors are themselves amplified by ligation of the LT receptors. An alternative paradigm is exemplified by the fact that LTB<sub>4</sub> enhanced the activation of the non-receptor protein tyrosine kinase Syk, a process evoked by IgG ligation of Fcγ and which is essential for phagocytosis, but was not capable of directly activating Syk in the absence of Fcγ ligation (48).

**Microbial killing.** In addition to their effects on phagocytosis, LTs have been shown to augment killing of a variety of microorganisms, including bacteria (33, 34), mycobacteria (14), fungi (49), and parasites (50, 51). Phagocytic cells utilize a myriad of microbicidal mechanisms to kill ingested microorganisms and many of these are activated or amplified by LTs. Lysosomal enzyme release was stimulated by LTB<sub>4</sub> (52). LTB<sub>4</sub> also induced the release of the antimicrobial peptide α-defensin by human neutrophils (53). Both LTB<sub>4</sub> and cysLTs induced NO generation in human neutrophils (54, 55) and 5-LO inhibitors decreased NO formation by elicited macrophages (56). Finally, the rapid generation of reactive oxygen intermediates upon assembly of the NADPH oxidase complex has been reported to be triggered by both LTB<sub>4</sub> (57) and cysLTs (55) in human neutrophils, as well as in alveolar macrophages (C. H. Serezani, D. M. Aronoff, S. Janear, P. Mancuso, and M. Peters-Golden, unpublished observations). Again, the intracellular signals required for NADPH oxidase activation appear to intersect with those generated by LT receptor ligation.

**Generation of other inflammatory mediators.** In addition to their direct actions on leukocyte effector functions discussed above, 5-LO metabolites also promote innate immune responses indirectly by stimulating the elaboration of other inflammatory mediators, such as cytokines and chemokines, which themselves activate leukocyte recruitment and antimicrobial mechanisms. Examples of this phenomenon include the ability of LTB<sub>4</sub> to induce lung generation of TNF-α (58), MCP-1 by monocytes (59), and IL-8 by neutrophils (60), and of cysLTs to stimulate production of IL-5, TNF-α and MIP-1 β by mast cells (61).

#### *Modulation of LT synthesis by other mediators of innate immunity*

LT synthetic capacity is under genetic control (62), but it is also subject to regulation by a vast array of endogenous (cytokines, hormones, small molecules, reactive species) and exogenous (toxins, pharmacologic agents, dietary factors) factors. Only a few of these with particular relevance to innate immunity will be discussed here.

**Colony-stimulating factors.** In addition to their originally recognized roles in myelopoiesis, G-CSF and GM-CSF are also recognized to up-regulate leukocyte functional responses, such as the recruitment, survival, phagocytosis, and microbicidal activities of neutrophils, monocytes, and macrophages (63). A role in LT synthesis is demonstrated by the facts that macrophages from GM-CSF-deficient mice exhibit reduced LT synthesis (64), and exogenous addition of CSFs has been shown to enhance the capacity for LT biosynthesis in vitro (65, 66) and in vivo (49, 67).

**Nitric oxide.** Despite its participation in microbial killing, NO has the capacity to down-regulate inflammatory responses by reducing cytokine production (68) and neutrophil recruitment (69). Interestingly, NO has also been shown to reduce LT synthetic capacity in cultured alveolar macrophages (30, 70) and mast cells (32). Such an impairment in macrophage LT synthesis in vitro and in vivo (71), attributable to LPS induction of NO generation, may contribute to the increased susceptibility to secondary infection (72) observed in patients who survive an episode of sepsis.

**Leptin.** Leptin is a 16-kDa protein synthesized by adipocytes that was initially recognized for its role in the regulation of food intake and energy balance, but which has more recently been recognized to also influence inflammatory and immune processes (73). Macrophage LT synthesis was recently found to be reduced in leptin-deficient mice, and this defect was associated with impaired innate immune responses following intrapulmonary challenge with *K. pneumoniae* (74); the addition of exogenous leptin in vitro restored cellular LT synthetic capacity and the relevant enzymatic mechanisms have recently been identified (75).

#### *LT deficiency in states of immunosuppression*

It is increasingly apparent that a plethora of clinical circumstances are associated with an acquired defect in LT synthesis (Table II). Many of these circumstances are exceedingly common and well recognized. Others, such as vitamin D<sub>3</sub> deficiency, are common but less well appreciated (76). Most of these impair LT biosynthesis in cells throughout the body, whereas the effect of cigarette smoking is limited to lung cells (77). Many of these conditions are clearly associated with increased susceptibility to infections. Although the causal importance of a relative LT deficiency in such susceptibility remains to be established, it is possible that defects in LT synthesis represent a common pathway to impaired innate immunity. As examples of this phenomenon, HIV infection and malnutrition will be considered further.

**HIV infection.** Peripheral blood neutrophils (49, 78), monocytes (67), and alveolar macrophages (79) from patients with HIV infection have all been reported to manifest a profound

Table II. Conditions associated with acquired defects in LT synthetic capacity

Condition	Refs.
HIV infection	49, 67, 78, 79
Protein-calorie malnutrition	84, 85
Diabetes mellitus (hyperglycemia)	99
Cigarette smoking	77, 100
Vitamin D deficiency	88
Cirrhosis	101
Newborn period	102, 103
Postsepsis	71

defect in their capacity for stimulated LT generation. This defect was confined to the 5-LO pathway and was associated with reduced expression of 5-LO and FLAP. As the defect extends to neutrophils, which cannot be directly infected with the virus, it is likely that the dysregulation of 5-LO metabolism is the consequence of an altered milieu. Indeed, the impairments in cellular LT biosynthesis and FLAP expression were quantitatively related to the decrement in CD4 lymphocyte count (79); moreover, macrophages from CD4-depleted mice also demonstrated reduced FLAP expression and decreased cellular LT synthesis (80). These studies suggest that optimal FLAP expression and LT synthetic capacity in myeloid cells in vivo depends on mediators elaborated by CD4 cells. In vivo data in humans support a role in this regard for CSFs. When subjects with end-stage AIDS (CD4 counts  $<100/\text{cm}^2$ ) were treated systemically for 5 days, GM-CSF (67) and G-CSF (49) were found to augment LT synthesis as well as 5-LO and FLAP expression in monocytes and neutrophils, respectively. In neutrophils, these effects were paralleled by increased capacity to kill fungi. That the augmented microbicidal activity was due to the increment in LT synthesis was indicated by the fact that it was completely abrogated by inclusion of a LT synthesis inhibitor (49).

An early report noted that *Pneumocystis* pneumonia in patients with HIV infection was associated with less lung neutrophilia than observed in patients with this infection and other states of immunosuppression (81), and it is possible that the blunted neutrophil accumulation in HIV-infected individuals relates to this alveolar macrophage defect in LTB<sub>4</sub> biosynthesis. Indeed, subsequent studies have explicitly documented unexpectedly low local levels of LTB<sub>4</sub> in bacterial pneumonia (82) as well as fungal meningitis (83) in HIV-positive individuals. It is also attractive to consider that this state of LT deficiency also contributes to impaired microbicidal capacity in HIV infection.

**Malnutrition.** Malnutrition is a vitally important cause of immunosuppression that affects both individuals in the developing world and those in industrialized countries. Both macronutrient (protein) and micronutrient (vitamin) deficiencies have been associated with impaired innate immunity. Experimental protein-calorie malnutrition in rats resulted in impaired production of LTB<sub>4</sub> by alveolar macrophages (84). In studies of undernourished hospitalized patients, LT synthesis by granulocytes was decreased as compared with cells from healthy controls (85). It is established that serum leptin levels decline rapidly during periods of caloric insufficiency (86), and it is likely that leptin deficiency during malnutrition is an important cause of defective LT synthesis and its associated immunosuppression. Deficiency of vitamin D<sub>3</sub> is known to be associated with an increased incidence of infections (87); of note, dietary vitamin D<sub>3</sub> deficiency in rats resulted in reduced LT synthetic capacity by macrophages (88), while exogenous vitamin D<sub>3</sub> increased FLAP expression and 5-LO metabolism (89).

#### *Therapeutic Implications*

We are aware of no evidence that anti-LT drugs used in the treatment of asthma have been associated with an increased incidence of infections of the respiratory tract or other organs. For a variety of reasons, however, this experience does not represent an adequate test of the role of LTs in innate immunity in vivo. First, the great bulk of such patients has been treated with cysLT1 antagonists; since the antimicrobial actions of cysLTs are narrower than those of LTB<sub>4</sub>, this approach may underes-

timate the impact that might be observed with drugs inhibiting LTB<sub>4</sub> synthesis or actions. Second, the incomplete abrogation of LT synthesis or actions achieved by currently available pharmacologic agents in a patient population known to be overproducing LTs would be expected to render these patients only relatively, but not absolutely, deficient in LTs. Finally, asthmatics do not have an intrinsically high susceptibility to bacterial or fungal infection. For all of these reasons, substantial blockade of LTs, especially LTB<sub>4</sub>, in a patient population with a recognized predilection for such infections might be necessary to reveal an important role for these molecules in innate immune responses. Future application of more potent LT biosynthesis inhibitors or LTB<sub>4</sub> antagonists in patients with disorders such as chronic obstructive lung disease, cystic fibrosis, acute lung injury, or organ transplantation may yet disclose such a role.

It is also of interest to ask whether commonly used medications might have unintended effects on LT synthesis and, thereby, on innate immunity. Increases in intracellular levels of cAMP can inhibit LT synthesis by a variety of enzymatic mechanisms (90), and commonly used cAMP-elevating drugs such as  $\beta$ -adrenergic agonists, theophylline, and phosphodiesterase inhibitors have been reported to inhibit LT synthesis by leukocytes (91). Although its clinical significance is unclear, in vivo cAMP elevation has been reported to impair pulmonary bacterial clearance in an animal model of pneumonia (92). It must be noted, however, that elevated intracellular cAMP can itself suppress antimicrobial functions of phagocytes (93); therefore, the contribution of reduced LT biosynthesis in this context is uncertain. By contrast, nonsteroidal anti-inflammatory drugs are capable of increasing LT synthesis in vivo, in part by diverting AA from the inhibited cyclooxygenase to the 5-LO pathway; interestingly, these medications have been associated with enhanced microbial clearance in animal models of infection (94), but once more the relative contribution of decreased generation of cAMP-elevating PGE<sub>2</sub> vs increased generation of 5-LO products cannot be distinguished. Finally, the antifungal agent amphotericin B has been reported to inhibit neutrophil 5-LO metabolism (95), and one wonders whether this potentially undesirable action extends to other antimicrobials.

Lastly, in view of the fact that a relative state of LT deficiency characterizes many conditions associated with increased susceptibility to infection, the possibility that stimulation of innate immunity might be accomplished by augmenting tissue levels of LTs merits consideration. In fact, it can be suggested that enhancing levels of LT biosynthesis may indirectly contribute to the immunostimulation resulting from administering cytokines such as CSFs (Ref. 96 and see above). Alternatively, tissue levels of LTs at a site of infection might be amplified by their direct administration. In this scenario, LTB<sub>4</sub> would be the preferred candidate for exogenous delivery because of its broader antimicrobial activity and lesser propensity for myotropic and edemagenic effects than cysLTs. LTB<sub>4</sub> was recently administered as an i.v. bolus to normal subjects and was shown to dose-dependently increase plasma levels of the antibacterial peptide  $\alpha$ -defensin and the chemokine MIP-1 $\beta$  (53). Local LTB<sub>4</sub> administration has been shown to reduce the peritoneal burden of bacteria in an animal model of peritonitis (33), and it has also been administered to the human lung via aerosol (97) or via a bronchoscope (98) and resulted in neutrophil influx without evidence of lung injury or other adverse effects. As compared with administration of a protein, direct administration of a lipid

such as LTB<sub>4</sub> has the advantages of being less immunogenic, shorter-lived, and less expensive.

### Conclusions

A growing body of evidence reviewed herein supports the conclusion that LTs are important participants in innate immune responses. Notable features of these mediators include their ability to be synthesized both rapidly and in delayed fashion by a variety of cell types, their diverse antimicrobial actions, and their network of interactions with many other relevant mediators. As compared with cytokines and chemokines, however, their role in antimicrobial defense has been largely overlooked. This likely reflects the commonly held but narrow view that lipid mediators are exclusively pathogenic and the corresponding ethos mandating their pharmacologic blockade that has dominated the pharmaceutical industry. A more enlightened contemporary perspective is needed to recognize the potential homeostatic functions of selected lipids, such as LTB<sub>4</sub> in innate immunity, and to seek to exploit these for therapeutic gain.

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