The Journal of Immunology

REVIEW ARTICLE | JANUARY 15 2005

Leukotrienes: Underappreciated Mediators of Innate Immune Responses[1]

Marc Peters-Golden; ... et. al

J Immunol (2005) 174 (2): 589–594.
https://doi.org/10.4049/jimmunol.174.2.589

THE JOURNAL OF IMMUNOLOGY

BRIEF REVIEWS

Leukotrienes: Underappreciated Mediators of Innate Immune Responses[1]

Marc Peters-Golden,[2] Claudio Canetti,* Peter Mancuso,† and Michael J. Coffey**

***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.**

Because myeloid cells contain substantial amounts of esterified arachidonic acid (AA)[3] 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_2 enzymes capable of liberating AA from membrane phospholipids, cytosolic phospholipase A_2 ($cPLA_2$) 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_4. Of note, activation of both $cPLA_2$ and 5-LO enzymes involves increases in intracellular calcium and is further enhanced by activation of certain protein kinases (5). LTA_4 is then hydrolyzed by LTA_4 hydrolase to LTB_4 or conjugated with reduced glutathione by LTC_4 synthase to form LTC_4. LTB_4 is best known as a leukocyte chemoattractant and activator, and LTC_4 is the parent compound of the cysteinyl LTs (cysLTs), which also include LTD_4 and LTE_4, 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_4, 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_4 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 Gq- and Gi-coupled receptors that modulate downstream signaling pathways involving phospholipase C/intracellular Ca^{2+}/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

Departments of *Internal Medicine (Division of Pulmonary and Critical Care Medicine) and †Environmental Health Sciences, University of Michigan, Ann Arbor, MI 48109

Received for publication September 20, 2004. Accepted for publication October 18, 2004.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

[1] This work was supported by National Institutes of Health Grant HL58897 and Conselho Nacional de Pesquisa-Brazil.

[2] Address correspondence and reprint requests to Dr. Marc Peters-Golden, Department of Internal Medicine, Division of Pulmonary and Critical Care Medicine, 6301 MSRB III, 1150 West Medical Center Drive, Ann Arbor, MI 48109-0642. E-mail address: petersm@umich.edu

[3] Abbreviations used in this paper: AA, arachidonic acid; LO, lipoxygenase; LT, leukotriene; $cPLA_2$, cytosolic phospholipase A_2; FLAP, 5-LO-activating protein; cysLT, cysteinyl LT; BLT, B leukotriene; PAMP, pathogen-associated molecular pattern; CR, complement receptor.

0022-1767/05/$02.00

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

	cysLT	LTB_4
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 Fcγ receptors triggers AA release and LT synthesis (12, 13), and this is to be expected in view of the well-documented capacity of Fcγ 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-κB-dependent genes and the synthesis of inflammatory mediators, such as TNF-α 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_2 (31).

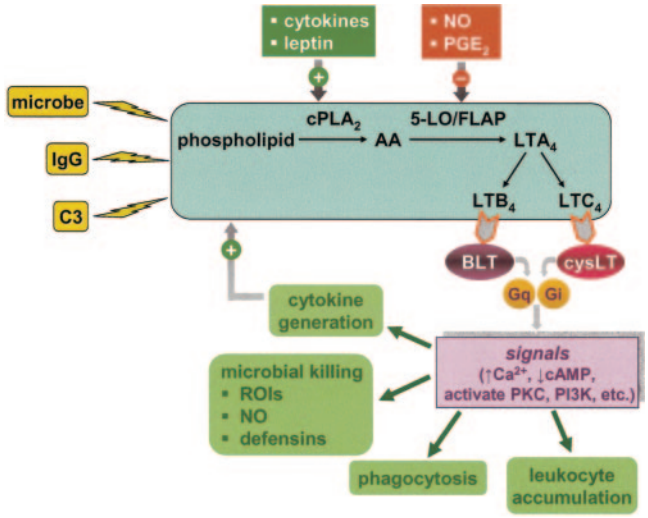

FIGURE 1. Synthesis and antimicrobial mechanisms of action of LTs. Microbes as well as opsonins IgG and C can trigger release of AA from membrane phospholipids and its metabolism to LTs. Neutrophils produce primarily LTB_4 and macrophages produce both classes of LTs. The expression and catalytic activity of these biosynthetic enzymes are influenced by relevant exogenous factors, with cytokines and leptin generally augmenting (indicated by "+") and NO and PGE_2 generally inhibiting (indicated by "−") LT production. By ligating BLT1/2 and cysLT1/2, LTB_4 and cysLTs activate Gq and Gi proteins to generate increased intracellular Ca^{2+} 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_4 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_4 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_4 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_4 (45) and LTC_4 (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_4 (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_4 (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_4 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_4 (52). LTB_4 also induced the release of the antimicrobial peptide α-defensin by human neutrophils (53). Both LTB_4 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_4 (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_4 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_3 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 $<100/cm^2$) 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_4 biosynthesis. Indeed, subsequent studies have explicitly documented unexpectedly low local levels of LTB_4 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_4 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_3 is known to be associated with an increased incidence of infections (87); of note, dietary vitamin D_3 deficiency in rats resulted in reduced LT synthetic capacity by macrophages (88), while exogenous vitamin D_3 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_4, this approach may underestimate the impact that might be observed with drugs inhibiting LTB_4 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_4, 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_4 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 β-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_2 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_4 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_4 was recently administered as an i.v. bolus to normal subjects and was shown to dose-dependently increase plasma levels of the antibacterial peptide α-defensin and the chemokine MIP-1β (53). Local LTB_4 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_4 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_4 in innate immunity, and to seek to exploit these for therapeutic gain.

Acknowledgments

We thank David Aronoff for critical review of this manuscript.

References

1. Lewis, R. A., K. F. Austen, and R. J. Soberman. 1990. Leukotrienes and other products of the 5-lipoxygenase pathway: biochemistry and relation to pathobiology in human disease. *N. Engl. J. Med. 323:645*.
2. Funk, C. 2001. Prostaglandins and leukotrienes: advances in eicosanoid biology. *Science 294:1871*.
3. Kanaoka, Y., and J. A. Boyce. 2004. Cysteinyl leukotrienes and their receptors: cellular distribution and function in immune and inflammatory responses. *J. Immunol. 173:1503*.
4. Diaz, B. L., and J. P. Arm. 2003. Phospholipase A_2. *Prostaglandins Leukot. Essent. Fatty Acids 69:87*.
5. Peters-Golden, M., and T. G. Brock. 2003. 5-lipoxygenase and FLAP. *Prostaglandins Leukot. Essent. Fatty Acids 69:99*.
6. Tager, A. M., and A. D. Luster. 2003. BLT1 and BLT2: the leukotriene B_4 receptors. *Prostaglandins Leukot. Essent. Fatty Acids 69:123*.
7. Hopkins, H., T. Stull, S. Von Essen, R. Robbins, and S. Rennard. 1989. Neutrophil chemotactic factors in bacterial pneumonia. *Chest 95:1021*.
8. Volovitz, B., R. Welliver, G. De Castro, D. Krystofik, and P. Ogra. 1988. The release of leukotrienes in the respiratory tract during infection with respiratory syncytial virus: role in obstructive airway disease. *Pediatr. Res. 24:504*.
9. Qadri, F., R. Raqib, F. Ahmed, T. Rahman, C. Wenneras, S. K. Das, N. H. Alam, M. M. Mathan, and A. M. Svennerholm. 2002. Increased levels of inflammatory mediators in children and adults infected with *Vibrio cholerae* O1 and O139. *Clin. Diagn. Lab. Immunol. 9:221*.
10. Kasirga, E., I. Coker, S. Aydogdu, R. V. Yagci, B. Taneli, and A. Gousseinov. 1999. Increased gastric juice leukotriene B_4, C_4 and E_4 concentrations in children with *Helicobacter pylori* colonization. *Turk J. Pediatr. 41:335*.
11. Gentile, D. A., P. Fireman, and D. P. Skoner. 2003. Elevations of local leukotriene C_4 levels during viral upper respiratory tract infections. *Ann. Allergy Asthma Immunol. 91:270*.
12. Mancuso, P., T. Standiford, T. Marshall, and M. Peters-Golden. 1998. 5-Lipoxygenase reaction products modulate rat alveolar macrophage phagocytosis of *Klebsiella pneumoniae*. *Infect. Immun. 66:5140*.
13. Claesson, H., J. Lindgren, and B. Gustafsson. 1985. Opsonized bacteria stimulate leukotriene synthesis in human leukocytes. *Biochim. Biophys. Acta 836:361*.
14. Coffey, M. J., S. M. Phare, and M. Peters-Golden. 2004. Role of leukotrienes in killing of Mycobacterium bovis by neutrophils. *Prostaglandins Leukot. Essent. Fatty Acids. 71:185*.
15. Locksley, R., J. Fankhauser, and W. Henderson. 1985. Alteration of leukotriene release by macrophages ingesting *Toxoplasma gondii*. *Proc. Natl. Acad. Sci. USA 82:6922*.
16. Castro, M., T. I. Morgenthaler, O. A. Hoffman, J. E. Standing, M. S. Rohrbach, and A. H. Limper. 1993. *Pneumocystis carinii* induces the release of arachidonic acid and its metabolites from alveolar macrophages. *Am. J. Respir. Cell Mol. Biol. 9:73*.
17. Wolf, J. E., S. E. Massof, and S. P. Peters. 1992. Alterations in murine macrophage arachidonic acid metabolism following ingestion of nonviable *Histoplasma capsulatum*. *Infect. Immun. 60:2559*.
18. Hennet, T., H. J. Ziltener, K. Frei, and E. Peterhans. 1992. A kinetic study of immune mediators in the lungs of mice infected with influenza A virus. *J. Immunol. 149:932*.
19. Gosselin, J., and P. Borgeat. 1997. Epstein-Barr virus modulates 5-lipoxygenase product synthesis in human peripheral blood mononuclear cells. *Blood 89:2122*.
20. Malaviya, R., and S. N. Abraham. 2000. Role of mast cell leukotrienes in neutrophil recruitment and bacterial clearance in infectious peritonitis. *J. Leukocyte Biol. 67:841*.
21. Moqbel, R., A. J. Macdonald, O. Cromwell, and A. B. Kay. 1990. Release of leukotriene C_4 (LTC_4) from human eosinophils following adherence to IgE- and IgG-coated schistosomula of Schistosoma mansoni. *Immunology 69:435*.
22. Greenberg, S., and S. Grinstein. 2002. Phagocytosis and innate immunity. *Curr. Opin. Immunol. 14:136*.
23. Fernandez, N., M. Renedo, S. Alonso, and M. S. Crespo. 2003. Release of arachidonic acid by stimulation of opsonic receptors in human monocytes: the FcγR and the complement receptor 3 pathways. *J. Biol. Chem. 278:52179*.
24. Claesson, H.-E., U. Lundberg, and C. Malmsten. 1981. Serum-coated zymosan stimulates the synthesis of leukotriene B_4 in human polymorphonuclear leukocytes. *Biochem. Biophys. Res. Commun. 99:1230*.
25. Rouzer, C., W. Scott, A. Hamill, and Z. Cohn. 1982. Synthesis of leukotriene C and other arachidonic acid metabolites by mouse pulmonary macrophages. *J. Exp. Med. 155:720*.
26. Akira, S., and K. Takeda. 2004. Toll-like receptor signalling. *Nat. Rev. Immunol. 4:499*.
27. Kimura, K., M. Shiota, K. Mochizuki, M. Ohta, and T. Sugano. 1992. Different preparations of zymosan induce glycogenolysis independently in the perfused rat liver: involvement of mannose receptors, peptide-leukotrienes and prostaglandins. *Biochem. J. 283:773*.
28. McCurdy, J. D., T. J. Olynych, L. H. Maher, and J. S. Marshall. 2003. Cutting edge: distinct Toll-like receptor 2 activators selectively induce different classes of mediator production from human mast cells. *J. Immunol. 170:1625*.
29. Aderem, A., D. Cohen, S. Wright, and Z. Cohn. 1986. Bacterial lipopolysaccharides prime macrophages for enhanced release of arachidonic acid metabolites. *J. Exp. Med. 164:165*.
30. Coffey, M., S. Phare, and M. Peters-Golden. 2000. Prolonged exposure to lipopolysaccharide inhibits macrophage 5-lipoxygenase metabolism via induction of nitric oxide synthesis. *J. Immunol. 165:3592*.
31. Brock, T. G., R. W. McNish, P. Mancuso, M. J. Coffey, and M. Peters-Golden. 2003. Prolonged lipopolysaccharide inhibits leukotriene synthesis in peritoneal macrophages: mediation by nitric oxide and prostaglandins. *Prostaglandins Other Lipid Mediat. 71:131*.
32. Gilchrist, M., S. D. McCauley, and A. D. Befus. 2004. Expression, localization, and regulation of NOS in human mast cell lines: effects on leukotriene production. *Blood 104:462*.
33. Demitsu, T., H. Katayama, T. Saito-Taki, H. Yaoita, and M. Nakano. 1989. Phagocytosis and bactericidal action of mouse peritoneal macrophages treated with leukotriene B_4. *Int. J. Immunopharmacol. 11:801*.
34. Bailie, M., T. Standiford, L. Laichalk, M. Coffey, R. Strieter, and M. Peters-Golden. 1996. Leukotriene-deficient mice manifest enhanced lethality from *Klebsiella pneumoniae* in association with decreased alveolar macrophage phagocytic and bactericidal activities. *J. Immunol. 157:5221*.
35. Medeiros, A. I., A. Sa-Nunes, E. G. Soares, C. M. Peres, C. L. Silva, and L. H. Faccioli. 2004. Blockade of endogenous leukotrienes exacerbates pulmonary histoplasmosis. *Infect. Immun. 72:1637*.
36. Chen, N., A. Restivo, and C. S. Reiss. 2001. Leukotrienes play protective roles early during experimental VSV encephalitis. *J. Neuroimmunol. 120:94*.
37. Ford-Hutchinson, A., M. Bray, and M. Doig. 1980. Leukotriene B_4, a potent chemokinetic and aggregating substance released from polymorphonuclear leukocytes. *Nature 286:264*.
38. Tager, A. M., S. K. Bromley, B. D. Medoff, S. A. Islam, S. D. Bercury, E. B. Friedrich, A. D. Carafone, R. E. Gerszten, and A. D. Luster. 2003. Leukotriene B_4 receptor BLT1 mediates early effector T cell recruitment. *Nat. Immunol. 4:982*.
39. Parameswaran, K., H. Liang, A. Fanat, R. Watson, D. P. Snider, and M. O. b. P. 2004. Role for cysteinyl leukotrienes in allergen-induced change in circulating dendritic cell number in asthma. *J. Allergy Clin. Immunol. 114:73*.
40. Robbiani, D., R. Finch, D. Jager, W. Muller, A. Sartorelli, and G. Randolph. 2000. The leukotriene C_4 transporter MRP1 regulates CCL19 (MIP-3β, ELC)-dependent mobilization of dendritic cells to lymph nodes. *Cell 103:757*.
41. Maekawa, A., K. F. Austen, and Y. Kanaoka. 2002. Targeted gene disruption reveals the role of cysteinyl leukotriene 1 receptor in the enhanced vascular permeability of mice undergoing acute inflammatory responses. *J. Biol. Chem. 277:20820*.
42. Shi, Z. Z., B. Han, G. M. Habib, M. M. Matzuk, and M. W. Lieberman. 2001. Disruption of γ-glutamyl leukotrienase results in disruption of leukotriene D_4 synthesis in vivo and attenuation of the acute inflammatory response. *Mol. Cell. Biol. 21:5389*.
43. Hebert, M.-J., T. Takano, H. Holthofer, and H. Brady. 1996. Sequential morphologic events during apoptosis of human neutrophils: modulation by lipoxygenase-derived eicosanoids. *J. Immunol. 157:3105*.
44. Lee, E., T. Robertson, J. Smith, and S. Kilfeather. 2000. Leukotriene receptor antagonists and synthesis inhibitors reverse survival in eosinophils of asthmatic individuals. *Am. J. Respir. Crit. Care Med. 161:1881*.
45. Wirth, J. J., and F. Kierszenbaum. 1985. Stimulatory effects of leukotriene B_4 on macrophage association with and intracellular destruction of Trypanosoma cruzi. *J. Immunol. 134:1989*.
46. Wirth, J. J., and F. Kierszenbaum. 1985. Effects of leukotriene C_4 on macrophage association with and intracellular fate of *Trypanosoma cruzi*. *Mol. Biochem. Parasitol. 15:1*.
47. Mancuso, P., P. Nana-Sinkam, and M. Peters-Golden. 2001. Leukotriene B_4 augments neutrophil phagocytosis of *Klebsiella pneumoniae*. *Infect. Immun. 69:2011*.
48. Canetti, C., B. Hu, J. L. Curtis, and M. Peters-Golden. 2003. Syk activation is a leukotriene B_4-regulated event involved in macrophage phagocytosis of IgG-coated targets but not apoptotic cells. *Blood 102:1877*.
49. Coffey, M., S. Phare, S. George, M. Peters-Golden, and P. Kazanjian. 1998. Granulocyte colony-stimulating factor administration to HIV-infected subjects augments

reduced leukotriene synthesis and anticryptococcal activity in neutrophils. *J. Clin. Invest. 102:663*.
50. Yong, E. C., E. Y. Chi, and W. R. Henderson, Jr. 1994. *Toxoplasma gondii* alters eicosanoid release by human mononuclear phagocytes: role of leukotrienes in interferon γ-induced antitoxoplasma activity. *J. Exp. Med. 180:1637*.
51. Talvani, A., F. S. Machado, G. C. Santana, A. Klein, L. Barcelos, J. S. Silva, and M. M. Teixeira. 2002. Leukotriene B_4 induces nitric oxide synthesis in *Trypanosoma cruzi*-infected murine macrophages and mediates resistance to infection. *Infect. Immun. 70:4247*.
52. Serhan, C., A. Radin, J. Smolen, H. Korchak, S. B., and G. Weissmann. 1982. Leukotriene B_4 is a complete secretagogue in human neutrophils: a kinetic analysis. *Biochem. Biophys. Res. Commun. 107:1006*.
53. Flamand, L., P. Borgeat, R. Lalonde, and J. Gosselin. 2004. Release of anti-HIV mediators after administration of leukotriene B_4 to humans. *J. Infect. Dis. 189:2001*.
54. Schmidt, H. H., R. Seifert, and E. Bohme. 1989. Formation and release of nitric oxide from human neutrophils and HL-60 cells induced by a chemotactic peptide, platelet activating factor and leukotriene B_4. *FEBS Lett. 244:357*.
55. Larfars, G., F. Lantoine, M. A. Devynck, J. Palmblad, and H. Gyllenhammar. 1999. Activation of nitric oxide release and oxidative metabolism by leukotrienes B_4, C_4, and D_4 in human polymorphonuclear leukocytes. *Blood 93:1399*.
56. Hubbard, N., and K. Erickson. 1995. Role of 5-lipoxygenase metabolites in the activation of peritoneal macrophages for tumoricidal function. *Mol. Immunol. 160:115*.
57. Dewald, B., and M. Baggiolini. 1985. Activation of NADPH oxidase in human neutrophils: synergism between fMLP and the neutrophil products PAF and LTB_4. *Biochem. Biophys. Res. Commun. 128:297*.
58. Goldman, G., R. Welbourn, L. Kobzik, C. R. Valeri, D. Shepro, and H. B. Hechtman. 1993. Lavage with leukotriene B_4 induces lung generation of tumor necrosis factor-α that in turn mediates neutrophil diapedesis. *Surgery 113:297*.
59. Huang, L., A. Zhao, F. Wong, J. M. Ayala, M. Struthers, F. Ujjainwalla, S. D. Wright, M. S. Springer, J. Evans, and J. Cui. 2004. Leukotriene B_4 strongly increases monocyte chemoattractant protein-1 in human monocytes. *Arterioscler. Thromb. Vasc. Biol. 24:1783*.
60. Kuhns, D. B., E. L. Nelson, W. G. Alvord, and J. I. Gallin. 2001. Fibrinogen induces IL-8 synthesis in human neutrophils stimulated with formyl-methionyl-leucyl-phenylalanine or leukotriene B_4. *J. Immunol. 167:2869*.
61. Mellor, E. A., K. F. Austen, and J. A. Boyce. 2002. Cysteinyl leukotrienes and uridine diphosphate induce cytokine generation by human mast cells through an interleukin 4-regulated pathway that is inhibited by leukotriene receptor antagonists. *J. Exp. Med. 195:583*.
62. Helgadottir, A., A. Manolescu, G. Thorleifsson, S. Gretarsdottir, H. Jonsdottir, U. Thorsteinsdottir, N. J. Samani, G. Gudmundsson, S. F. Grant, G. Thorgeirsson, et al. 2004. The gene encoding 5-lipoxygenase activating protein confers risk of myocardial infarction and stroke. *Nat. Genet. 36:233*.
63. Weisbart, R. H., J. C. Gasson, and D. W. Golde. 1989. Colony-stimulating factors and host defense. *Ann, Intern. Med. 110:297*.
64. Paine, R. III, S. B. Morris, H. Jin, S. E. Wilcoxen, S. M. Phare, B. B. Moore, M. J. Coffey, and G. B. Toews. 2001. Impaired functional activity of alveolar macrophages from GM-CSF-deficient mice. *Am. J. Physiol. 281:L1210*.
65. Brock, T. G., R. W. McNish, M. J. Coffey, T. C. Ojo, S. M. Phare, and M. Peters-Golden. 1996. Effect of granulocyte-macrophage colony-stimulating factor on eicosanoid production by mononuclear phagocytes. *J. Immunol. 156:2522*.
66. Pouliot, M., P. McDonald, P. Borgeat, and S. McColl. 1994. Granulocyte/macrophage colony-stimulating factor stimulates the expression of the 5-lipoxygenase-activating protein (FLAP) in human neutrophils. *J. Exp. Med. 179:1225*.
67. Coffey, M., S. Phare, S. Cinti, M. Peters-Golden, and P. Kazanjian. 1999. Granulocyte-macrophage colony-stimulating factor upregulates reduced 5-lipoxygenase metabolism in peripheral blood monocytes and neutrophils in AIDS. *Blood 94:3897*.
68. Thomassen, M. J., L. T. Buhrow, M. J. Connors, F. T. Kaneko, S. C. Erzurum, and M. S. Kavuru. 1997. Nitric oxide inhibits inflammatory cytokine production by human alveolar macrophages. *Am. J. Respir. Cell Mol. Biol. 17:279*.
69. Benjamim, C. F., S. H. Ferreira, and F. Q. Cunha. 2000. Role of nitric oxide in the failure of neutrophil migration in sepsis. *J. Infect. Dis. 182:214*.
70. Brunn, G., C. Hey, I. Wessler, and K. Racke. 1997. Endogenous nitric oxide inhibits leukotriene B_4 release from rat alveolar macrophages. *Eur. J. Pharmacol. 326:53*.
71. Coffey, M. J., S. M. Phare, and M. Peters-Golden. 2004. Induction of iNOS by LPS/interferon γ and sepsis downregulates 5-lipoxygenase metabolism in murine alveolar macrophages. *Exp. Lung Res. 30:615*.
72. Niederman, M., and A. Fein. 1990. Sepsis syndrome, the adult respiratory distress syndrome, and nosocomial pneumonia: a common clinical sequence. *Clin. Chest Med. 11:633*.
73. La Cava, A., and G. Matarese. 2004. The weight of leptin in immunity. *Nat. Rev. Immunol. 4:371*.
74. Mancuso, P., A. Gottschalk, S. M. Phare, M. Peters-Golden, N. W. Lukacs, and G. B. Huffnagle. 2002. Leptin-deficient mice exhibit impaired host defense in Gram-negative pneumonia. *J. Immunol. 168:4018*.
75. Mancuso, P., C. Canetti, A. Gottschalk, P. K. Tithof, and M. Peters-Golden. 2004. Leptin augments alveolar macrophage leukotriene synthesis by increasing phospholipase activity and enhancing group IVC iPLA$_2$ (cPLA$_{2\gamma}$) protein expression. *Am. J. Physiol. 287:L497*.
76. Calvo, M. S., and S. J. Whiting. 2003. Prevalence of vitamin D insufficiency in Canada and the United States: importance to health status and efficacy of current food fortification and dietary supplement use. *Nutr. Rev. 61:107*.
77. Balter, M., G. Toews, and M. Peters-Golden. 1989. Multiple defects in arachidonate metabolism in alveolar macrophages from young asymptomatic smokers. *J. Lab. Clin. Med. 114:662*.
78. Thorsen, S., M. Busch-Sorensen, and J. Sondergaard. 1989. Reduced neutrophil production of leukotriene B_4 associated with AIDS. *AIDS 3:651*.
79. Coffey, M., S. Phare, P. Kazanjian, and M. Peters-Golden. 1996. 5-Lipoxygenase metabolism in alveolar macrophages from subjects infected with the human immunodeficiency virus. *J. Immunol. 157:393*.
80. Coffey, M., S. Phare, M. Peters-Golden, and G. Huffnagle. 1999. Regulation of 5-lipoxygenase metabolism in mononuclear phagocytes by CD4 T lymphocytes. *Exp. Lung Res. 25:617*.
81. Limper, A., K. Offord, T. Smith, and W. I. Martin. 1989. Pneumocystis carinii pneumonia: differences in lung parasite number and inflammation in patients with and without AIDS. *Am. Rev. Respir. Dis. 140:1204*.
82. Krarup, E., J. Vestbo, T. Benfield, and J. Lundgren. 1997. Interleukin-8 and leukotriene B_4 in bronchoalveolar lavage fluid from HIV-infected patients with bacterial pneumonia. *Respir. Med. 91:317*.
83. Froldi, M., M. Parma, R. Marenzi, A. Piona, M. Lorini, E. Nobile Orazio, A. Castagna, and A. Lazzarin. 1995. Low levels of LTB_4 in cerebrospinal fluid of AIDS patients with cryptococcal meningitis. *J. Clin. Lab. Immunol. 47:41*.
84. Skerrett, S., W. Henderson, and T. Martin. 1990. Alveolar macrophage function in rats with severe protein calorie malnutrition: arachidonic acid metabolism, cytokine release, and antimicrobial activity. *J. Immunol. 144:1052*.
85. Cederholm, T., J. A. Lindgren, and J. Palmblad. 2000. Impaired leukotriene C_4 generation in granulocytes from protein-energy malnourished chronically ill elderly. *J. Intern. Med. 247:715*.
86. Fried, S. K., M. R. Ricci, C. D. Russell, and B. Laferrere. 2000. Regulation of leptin production in humans. *J. Nutr. 130:3127S*.
87. Muhe, L., S. Lulseged, K. E. Mason, and E. A. Simoes. 1997. Case-control study of the role of nutritional rickets in the risk of developing pneumonia in Ethiopian children. *Lancet 349:1801*.
88. Coffey, M. J., S. E. Wilcoxen, S. M. Phare, R. U. Simpson, M. R. Gyetko, and M. Peters-Golden. 1994. Reduced 5-lipoxygenase metabolism of arachidonic acid in macrophages from 1,25-dihydroxyvitamin D_3-deficient rats. *Prostaglandins 48:313*.
89. Coffey, M. J., M. Gyetko, and M. Peters-Golden. 1993. 1,25-Dihydroxyvitamin D_3 upregulates 5-lipoxygenase metabolism and 5-lipoxygenase activating protein in peripheral blood monocytes as they differentiate into mature macrophages. *J. Lipid Mediators 6:43*.
90. Luo, M., S. M. Jones, S. M. Phare, M. J. Coffey, M. Peters-Golden, and T. G. Brock. 2004. Protein kinase A inhibits leukotriene synthesis by phosphorylation of 5-lipoxygenase on serine 523. *J. Biol. Chem. 279:41512*.
91. Tenor, H., A. Hatzelmann, M. K. Church, C. Schudt, and J. K. Shute. 1996. Effects of theophylline and rolipram on leukotriene C_4 (LTC_4) synthesis and chemotaxis of human eosinophils from normal and atopic subjects. *Br. J. Pharmacol. 118:1727*.
92. Soares, A. C., D. G. Souza, V. Pinho, A. T. Vieira, M. M. Barsante, J. R. Nicoli, and M. Teixeira. 2003. Impaired host defense to *Klebsiella pneumoniae* infection in mice treated with the PDE_4 inhibitor rolipram. *Br. J. Pharmacol. 140:855*.
93. Aronoff, D. M., C. Canetti, and M. Peters-Golden. 2004. Prostaglandin E_2 inhibits alveolar macrophage phagocytosis through an E-prostanoid 2 receptor-mediated increase in intracellular cyclic AMP. *J. Immunol. 173:559*.
94. Campanile, F., A. Giampietri, U. Grohmann, L. Binaglia, M. C. Fioretti, and P. Puccetti. 1993. Accelerated hematopoietic recovery and protective effect of the cyclooxygenase inhibitor indomethacin in bacterial infection of neutropenic mice. *Cell. Immunol. 147:341*.
95. Shindo, K., M. Fukumura, and A. Ito. 1998. Inhibitory effect of amphotericin B on leukotriene B_4 synthesis in human neutrophils in vitro. *Prostaglandins Leukot. Essent. Fatty Acids 58:105*.
96. Kuritzkes, D. R. 2000. Neutropenia, neutrophil dysfunction, and bacterial infection in patients with human immunodeficiency virus disease: the role of granulocyte colony-stimulating factor. *Clin. Infect. Dis. 30:256*.
97. Sampson, S., J. Costello, and A. Sampson. 1997. The effect of inhaled leukotriene B_4 in normal and in asthmatic subjects. *Am. J. Respir. Crit. Care Med. 155:1789*.
98. Martin, T., B. Pistorese, E. Chi, R. Goodman, and M. Matthay. 1989. Effect of leukotriene B_4 in the human lung: recruitment of neutrophils into the alveolar spaces without a change in protein permeability. *J. Clin. Invest. 89:1009*.
99. Jubiz, W., R. Draper, J. Gale, and G. Nolan. 1984. Decreased leukotriene B_4 synthesis by polymorphonuclear leukocytes from male patients with diabetes mellitus. *Prostaglandins Leukot. Med. 14:305*.
100. Laviolette, M., R. Coulombe, S. Picard, P. Braquet, and P. Borgeat. 1986. Decreased leukotriene B_4 synthesis in smokers' alveolar macrophages in vitro. *J. Clin. Invest. 77:54*.
101. Claria, J., E. Titos, W. Jimenez, J. Ros, P. Gines, V. Arroyo, F. Rivera, and J. Rodes. 1998. Altered biosynthesis of leukotrienes and lipoxins and host defense disorders in patients with cirrhosis and ascites. *Gastroenterology 115:147*.
102. Lu, M.-C., M. Peters-Golden, D. Hostetler, N. Robinson, and F. Derksen. 1996 Age-related enhancement of 5-lipoxygenase metabolic capacity in cattle alveolar macrophages. *Am. J. Physiol. 271:L547*.
103. Chakraborti, T., M. Mandal, S. Das, and S. Chakraborti. 1999. Age-dependent change in arachidonic acid metabolic capacity in rat alveolar macrophages. *Biochem. Mol. Biol. Int. 47:501*.