Cell. Mol. Life Sci. 64 (2007) 2657 – 2670
1420-682X/07/192657-14
DOI 10.1007/s00018-007-7228-2

Cellular and Molecular Life Sciences

Review

Leukotrienes: Mediators that have been typecast as villains

N. Flamand[a], P. Mancuso[b], C. H. C. Serezani[a] and T. G. Brock[a,] *

[a] Department of Internal Medicine, University of Michigan, Ann Arbor, MI 48109 (USA),
e-mail: brocko@umich.edu
[b] Department of Environmental Health Sciences, University of Michigan, Ann Arbor, MI 48109 (USA)

Received 8 May 2007; received after revision 5 June 2007; accepted 26 June 2007
Online First 19 July 2007

Abstract. As befalls many mediators that act upon the human stage, leukotrienes have become identified with their most powerful roles as villains of the immune system. They are well known for their leading roles in allergic diseases, including asthma. They also have gained recognition for their dramatic role as promoters of inflammation. As new roles for these lipid messengers are sought, it is becoming apparent that the leukotrienes have been typecast as bad guys of the immune system. As examples, their more recent roles have been in atherosclerosis, pulmonary fibrosis and cancer. However, upon further evaluation, we can begin to see their versatility. Thus, leukotrienes stimulate innate immunity against pathogens. In addition, they promote the expression of mediators, receptors and other molecules that are important for immune defense. In these lesser known roles, they lead the fight against bacterial, fungal and viral infection. This review is intended to shed light on the leukotrienes, where they come from and what we really know about them.

Keywords. Arachidonic acid, 5-lipoxygenase, bronchoconstriction, inflammation, phagocytosis, gene expression, atherosclerosis.

Introduction

Leukotrienes (LTs) are chemical messengers that signal from cells of the immune system to essentially all other types of cells in the surrounding tissue. They are primarily produced by mature, differentiated leukocytes of either the granulocytic or mononuclear lineage, in part because these are the predominant cells that express the key proteins that are required for LT synthesis. LTs are known to have very powerful effects over short distances within the body.

Current research on LTs includes how they are synthesized and secreted, what receptors they activate on target cells and the second signals activated upon receptor ligation, the cellular responses to activation by LTs, and the consequences in terms of health and pathophysiology. This review presents features of our current knowledge regarding LTs and also discusses some of the emerging concepts that lead to excitement in the field of LT study.

Best-known roles for LTs

LTs are the immediate products of the 5-lipoxygenase (5-LO) pathway, so-called because the enzyme 5-LO initiates their synthesis, as described below. This pathway generates several distinct species of lipid mediators. However, the best-known LTs are LTB_4, LTC_4, LTD_4 and LTE_4. The last three of these have similar effects and are commonly referred to as

* Corresponding author.

cysteinyl LTs (cysLTs), as they have a cysteine residue in common.

As noted above, the LTs are made primarily by mature leukocytes, with the types of products depending on the cell type. Thus, human neutrophils, dendritic cells and B lymphocytes produce primarily LTB_4, human eosinophils secrete LTC_4, human mast cells make more LTC_4 than LTB_4, and human monocytes and macrophages synthesize more LTB_4 than LTC_4. Surprisingly, these patterns do not necessarily persist across animal species. For example, eosinophils from guinea pigs make abundant LTB_4 [1] and mouse macrophages make much more LTC_4 than LTB_4 [2]. In general, LTs are secreted from leukocytes and are analogous to hormones that act locally. As a result, they are said to have "paracrine" actions when their effects are on neighboring cells. LTs also have "autocrine" actions, as they affect the source cell itself. They initiate their effects by activating highly selective G protein-coupled receptors. Two such receptors have been described for LTB_4: BLT_1 and BLT_2. BLT_1 is a high-affinity receptor for LTB_4, responding optimally at concentrations of 1–100 nM [3]. In transfected cells overexpressing BLT_1, LTB_4 addition can activate Gi proteins and suppress cAMP signaling [3] or activate Gα proteins, activating phospholipase C [4]. BLT_2 responds to LTB_4 at concentrations greater than 10 nM, with maximal effect at 0.1–1.0 μM LTB_4 [5]. In addition to these two cell surface receptors, LTB_4 can bind PPARα *in vitro* [6] and activate it in cells [7].

As for LTB_4, two G protein-coupled receptors have been identified for the cysLTs and have been named the $CysLT_1$ and $CysLT_2$. The $CysLT_1$ receptor binds LTD_4 with high affinity (1–10 nM) and binds LTC_4 and LTE_4 with progressively lower affinities, whereas the $CysLT_2$ receptor binds LTC_4 and LTD_4 with equal affinity (K_d ~10 nM). In transfected cells overexpressing either $CysLT_1$ or the $CysLT_2$ receptor, ligand addition initiates calcium flux through PTX-resistant Gq proteins [8, 9]. More recently, the orphan receptor GPR17 has been shown to be activated by CysLTs as well as uracil nucleotides [10]; in cells overexpressing GPR17, but not $CysLT_1$ or $CysLT_2$, either LTC_4 or LTD_4 increased calcium influx and inhibited adenylyl cyclase. Activation of this receptor, as well as resulting brain injury in a rat focal ischemia model, were blocked by receptor blockers, suggesting roles for CysLTs and GPR17 in ischemic injury [10].

LTB_4 is best known for its role in initiating the inflammatory response. Produced by leukocytes (*e.g.*, macrophages) residing in the tissue in response to stimuli like infection or stress, LTB_4 potently promotes the adherence to endothelium [11], chemotaxis [12], and activation of neutrophils and other leukocytes [13, 14]. In this way, LTB_4 drives the recruitment of leukocytes from the bloodstream into tissues. Concomitant activation of the recruited leukocytes by LTB_4 triggers many important functions, including additional synthesis of LTB_4 by the recruited cells. One result is the dramatic increase in tissue cellularity, a hallmark of inflammation.

Because of its potent pro-inflammatory actions, LTB_4 has been considered to contribute to many different diseases that have inflammation as components. Thus, LTB_4 was long ago shown to be overproduced in ulcerative colitis or Crohn's disease [15, 16], inflammatory bowel disease [17], collagen-induced arthritis [18], rheumatoid arthritis [19], psoriasis [20] and cystic fibrosis [21]. While LTB_4 appears to be abundantly produced in these diseases, interest in understanding its role or the therapeutic benefits of blocking its synthesis or action has waned in recent years.

The cysLTs, LTC_4, LTD_4 and LTE_4, are best known for their potent bronchoconstricting effects, resulting from the contraction of airway smooth muscle [22]. Through this effect, cysLTs cause the airway constriction that is central to some forms of asthma. CysLTs also induce mucus secretion by bronchial mucosa [23], which is also a feature of asthma. In addition, cysLTs can also promote the constriction of both venous and arterial vascular smooth muscle [24, 25], playing a role in regulating vasoconstriction. CysLTs also directly affect endothelial cells to produce vascular leak of plasma into tissues [26, 27], resulting in edema that is characteristic of skin allergic reactions, allergic asthma and allergic rhinitis. Finally, cysLTs can attract and activate some leukocytes, especially eosinophils and monocytes, and in this way contribute to inflammation.

Many of the pathological effects of LTs are associated with their over-production. Thus, the difference between asthmatic individuals and non-asthmatics may be as simple as how much LTs are produced at a given time. For example, most non-asthmatics are familiar with a noticeable constriction of the airway following an extended period of intense exercise or after entering a smoke-filled room. This normal airway constriction may be compared with the much stronger response that can be incapacitating and perhaps life-threatening in an asthmatic. Because of the significance of LT over-production in disease, there remains much interest in understanding the regulation of LT synthesis.

LT synthesis: The 5-LO pathway

LTs, as well as other eicosanoids, can be produced rapidly from substrate, arachidonic acid (AA), that is stored in membrane phospholipids. This distinguishes

them from pre-formed mediators, like histamine or myeloperoxidase, which are retained in granules for immediate release upon cell stimulation, and cytokines, which typically require gene transcription and mRNA translation for production. This difference in method of production is a central reason to focus on the LT synthetic pathway, as opposed to, *e.g.*, degranulation or gene regulation, as a key point of regulation.

LT synthesis, of course, depends on AA availability. AA is an ω-6 polyunsaturated (20:4) fatty acid. AA derived from the diet is rapidly incorporated into the membranes of all cells in the body. The bulky size of this fatty acid may be one reason it is found predominantly in the sn-2 position of membrane phospholipids. Interestingly, upon arrival at the cell, AA is moved first to the nucleus and acylated into membranes of the nuclear envelope [28, 29]. Over several hours, with membrane remodeling, AA becomes dispersed throughout all the membranes of the cell. In the healthy individual, therefore, there exists a large pool of AA in the vast membrane system of all the cells of the body.

The release of stored AA is mediated by phospholipases (PLA), primarily by PLA_2 enzymes, which release fatty acids from the sn-2 phospholipid position. There are many PLA_2 isoforms with different properties and cell distributions that can release AA. The type IV PLA_2s, also known as cytosolic PLA_2 ($cPLA_2$s), play a major role in releasing AA for LT production [30]. Their activity is augmented by phosphorylation [31–33] and can be altered by changes in expression [34–37]. The low molecular weight PLA_2s, also known as secretory PLA_2s ($sPLA_2$s), can also be a primary source of AA [38]. They may be regulated by rate of secretion [39] or synthesis [39, 40].

Importantly, these PLA_2s can act in cells that lack the other enzymes that are necessary for LT synthesis. It is clear that AA released from these neighboring cells can be an important source of substrate for LT production [41]. Thus, AA that is stored in non-leukocytes (*e.g.*, epithelial cells) can be used in a transcellular fashion by leukocytes to produce LTs.

Free AA, derived from either internal stores or from neighboring cells, is first modified by the enzyme 5-lipoxygenase (5-LO), with the assistance of the 5-LO-activating protein FLAP (Fig. 1). 5-LO catalyzes two reactions, the insertion of molecular oxygen into AA to form 5-hydroperoxyeicosatetraenoic acid (5-HpETE) as well as its subsequent dehydration to LTA_4 [42, 43]. The intermediate 5-HpETE is often made in significant amounts. 5-HpETE is rapidly modified to 5-hydroxyeicosatetraenoic acid (5-HETE) by peroxidases, and 5-HETE can be further metabolized to 5-oxo-eicosatetraenoic acid (5-oxo-ETE) by 5-hydroxyeicosanoid dehydrogenase (5-HEDH). The end product of 5-LO action, LTA_4, can be either hydrolyzed by the enzyme LTA_4 hydrolase to give LTB_4 or conjugated with glutathione by the enzyme LTC_4 synthase to produce LTC_4. LTC_4 may be further metabolized to LTD_4 by the removal of the glutamate residue, which is mediated by peptidases including γ-glutamyl transferase. LTE_4 is produced from LTD_4 by the removal of glycine by peptidases. An important feature of the 5-LO pathway to LT synthesis is its activation. The 5-LO enzyme has a resting and activated state, so that there is no LT synthesis in normal leukocytes without stimulation. Many different factors can stimulate the cells and activate 5-LO, leading to LT synthesis. More importantly, different cues can lead to changes in the 5-LO pathway in the "resting" leukocytes, dramatically changing the amounts of LTs produced when 5-LO becomes activated (reviewed in [44, 45]). Also, there appear to be diseases where the 5-LO pathway is constitutively activated and LTs are constantly produced, as in aspirin-sensitive asthma [46] and in pulmonary fibrosis [47].

Additional roles for LTs as villains

Repeatedly over the last decade, LTs have easily been cast into roles as bad guys. A series of studies have given central roles to LTs in that most evil of diseases, cancer. A short list of several hundred of these studies includes cancers of the lung [48, 49], pancreas [50], bladder [51], prostate [52], kidney [53], esophagus [54], and colorectal region [55]. It remains to be seen whether any of these roles will be viewed as significant.

The development of LT-deficient mice, produced by disruption of the 5-LO gene to generate $5\text{-LO}^{-/-}$ mice, was achieved by two groups (by Funk and colleagues [56] and by Koller and colleagues [57]) independently in 1994. Studies using these mice, lacking 5-LO activity, again suggested deleterious roles for LTs. The $5\text{-LO}^{-/-}$ mice provided evidence that LTs contributed to inflammatory diseases, including zymosan-induced peritonitis [58], collagen- and autoantibody-induced arthritis [59, 60], pulmonary inflammation induced by IL-13 [61], and cerulein-induced pancreatitis [62]. Additionally, the 5-LO-deficient mice indicated that LTs were involved in the development of hypoxia-induced chronic pulmonary hypertension [63], airway hyperresponsiveness [64], lupus [65], allograft rejection [66], bleomycin-induced pulmonary fibrosis [67], and ischemia-reperfusion injuries [68, 69].

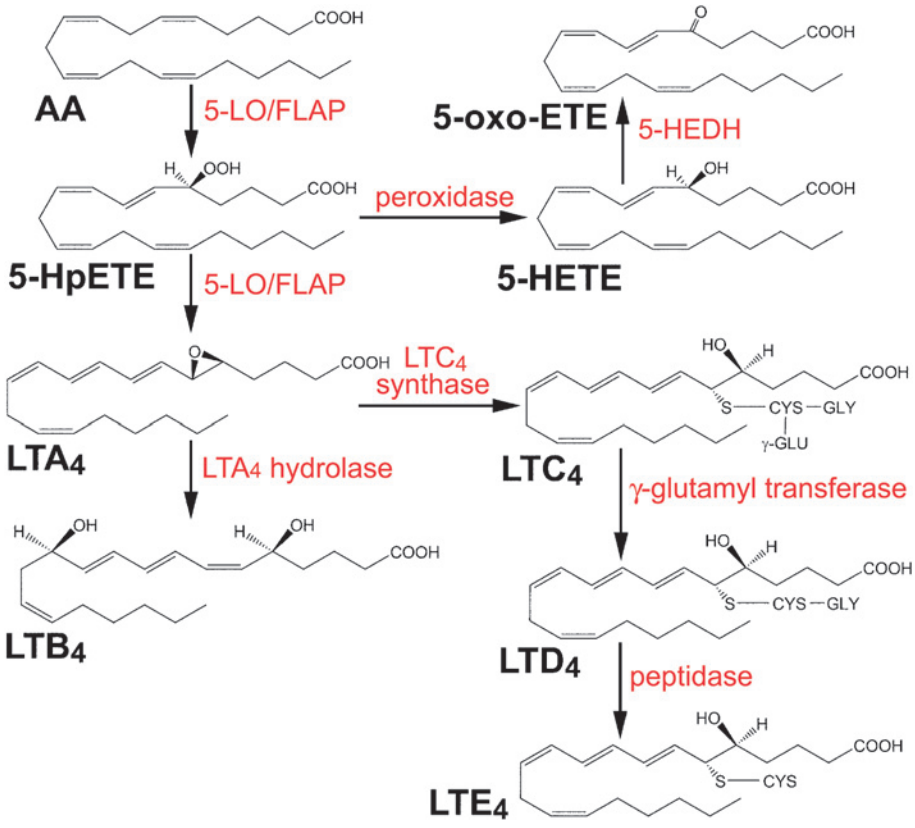

Figure 1. Biosynthesis of leukotrienes (LTs) *via* the 5-lipoxygenase (5-LO) pathway.

Obviously, studies using 5-LO$^{-/-}$ mice do not delineate the individual roles of LTB_4 or cysLTs. However, LTA_4 hydrolase$^{-/-}$ mice, which cannot produce LTB_4, have less inflammation in zymosan-induced peritonitis and are resistant to platelet-activating factor (PAF) signaling [70], showing a role for LTB_4. This resistance to PAF in LTA_4 hydrolase$^{-/-}$ mice further suggested a role for LTB_4 as an intermediary in PAF-induced systemic shock [70] as well as endotoxemia induced by PAF but not LPS-induced endotoxemia [56, 57]. Both LTB_4 and its BLT_1 receptor are necessary for the development of inflammatory arthritis in a mouse model [71, 72]. Apparently, both cysLTs and LTB_4 are involved in bleomycin-induced pulmonary fibrosis: while 5-LO$^{-/-}$ mice are totally protected, $CysLT_1^{-/-}$ mice develop a more severe fibrosis (associated with increased cysLT production) and both LTC_4 synthase$^{-/-}$ and $CysLT_2^{-/-}$ mice are only protected by ~50% [73, 74]. These studies suggest that LTB_4 and the cysLTs act in distinct and perhaps complementary roles in these mouse models.

Currently getting the greatest buzz in the research community is the villainous role for LTs in cardiovascular disease. Initial studies, examining a mouse strain that was resistant to atherosclerosis, identified the 5-LO gene as being important [75]. Human atherosclerotic tissues were found to show abundant 5-LO protein [76], suggesting that LTB_4 or cysLTs, or both, may contribute to pathogenesis. Studies in mice suggested that LTB_4 was important for smooth muscle remodeling in the context of atherogenesis [77, 78] and co-expression of 5-LO and LTA_4 hydrolase correlated with plaque instability in human lesions [79]. Moreover, the potent effects on cysLTs on gene expression in human endothelial cells [80], discussed below, suggest that cysLTs may be important in vascular disease. In particular, the up-regulation of the early growth response (egr) transcription factors induced in endothelial cell by cysLTs [80, 81] is recognized as a key step in angiogenesis and parallels the action of VEGF. Excellent reviews of the roles of LTs in cardiovascular disease are available [82–84].

LTs: Now starring as heroes in host defense

In a departure from their roles in allergen-induced inflammation and asthma, LTs are gaining recognition for their performances in host defense against infection. One way to illustrate the importance of LTs in host defense is to examine states of LT deficiency. Attenuated LT synthesis is correlated with an increased susceptibility to infectious disease in conditions including malnutrition [85–88], cigarette smok-

ing [89, 90], vitamin D deficiency [91], HIV infection [92, 93], cirrhosis of the liver [94], and type II diabetes [95]. While the underlying cause of increased susceptibility to infectious disease in these conditions is complex and likely to involve innate immune response impairments that are independent of the LT synthetic pathway, studies using 5-LO-deficient mice and pharmacological LT synthesis inhibitors support the involvement of LTs in host defense against infectious agents (reviewed in [96]). However, there are as yet no reports, to our knowledge, indicating that the therapeutic use of anti-LT drugs increases one's susceptibility to infectious disease.

LT deficiency associated with increased susceptibility to infectious disease has been described in a number of murine models of pulmonary infection. Bailie and coworkers [97] were the first to show that 5-LO$^{-/-}$ mice exhibit increased susceptibility to gram-negative pneumonia. In this report, 5-LO$^{-/-}$ mice demonstrated increased mortality and impaired pulmonary bacterial clearance following *Klebsiella pneumoniae* challenge. This cast LTs in the role of heroes in the fight against bacteria. Additional roles for LTs in fighting infection followed. Pharmacological inhibition of LT synthesis *in vivo*, using A-63162, impaired peritoneal clearance of *E. coli* in a murine model of infectious peritonitis [98]. Similarly, higher levels of bacteria were found in the peritoneal cavities of 5-LO$^{-/-}$ mice, compared with wild-type controls, in the cecal ligation and puncture model of peritonitis and sepsis [99]. Interestingly, 5-LO$^{-/-}$ mice were protected against *Mycobacterium tuberculosis* when infected with 50 or 300 CFU [100], while another recent study, involving inhibitors of the 5-LO pathway and performed with a much bigger bolus (10^5 CFU), suggested that the 5-LO pathway promoted host defense against this pathogen [101]. This suggested that LTs may be particularly important in larger infections.

LTs have also been found to have hero roles against other pathogens. Medeiros et al. [102] reported that survival and pulmonary clearance of the fungus *Histoplasmosis capsulatum* were reduced in mice treated with MK-886, a LT synthesis inhibitor. Also, intravenous injection of LTB_4 reduced viral loads and enhanced survival of mice given cytomegalovirus, whereas 5-LO$^{-/-}$ mice or mice treated with MK-886 had increased viral loads compared to wild-type, untreated mice [103], indicating that LTB_4 has antiviral activity. LT deficiency induced by the 5-LO inhibitor zileuton or by genetic means (5-LO$^{-/-}$ mice) suppressed the innate immune response of mice during the pathogenesis of vesicular stomatitis virus encephalitis [104]. Finally, it has been shown that LTB_4 synthesis influences resistance and susceptibility patterns to *Leishmania amazonensis* infection [105].

Resident macrophages and recruited leukocytes produce LTs following interaction with microbes *via* cell surface receptors for opsonins or pathogen-associated molecular patterns [96]. Organisms that are opsonized with IgG will interact with the Fcγ receptor expressed on the surface of leukocytes and activate the liberation of AA from tissue phospholipids and subsequent LT synthesis [106, 107]. LT synthesis can also be activated *via* the toll-like receptor 2 (TLR2) [108], by CD14/TLR4 agonists [109], *via* TLR8 [110] and through the β-glucan receptor [111].

The rapid recruitment of leukocytes to the site of infection is critical for mounting an effective host defense. Upon interacting with bacteria, macrophages elaborate LTB_4, the most abundant 5-LO product in cells from humans and rats, cysLTs, 5-HETE, and other metabolites but in much lower quantities [106, 112]. Other microorganisms, such as mycobacterial species [113], *Pneumocystis carinii* [114], *Histoplasma capsulatum* [115], and Epstein-Barr virus [116], activate macrophages or monocytes to produce different profiles of 5-LO products than what would be observed for cells stimulated with bacteria or zymosan [107, 110]. The LTs facilitate leukocyte recruitment through a number of different mechanisms. First, LTB_4 is a potent chemoattractant that recruits neutrophils and monocytes to the site of infection presumably by activating the leukocyte BLT_1 receptors that trigger actin polymerization [12, 71, 117]. Second, LTB_4 also contributes to leukocyte recruitment by up-regulating the expression of integrins on the surface of leukocytes enhancing their adherence to endothelial cells within the vasculature of infected tissues [118]. Third, the cysLTs may also facilitate leukocyte recruitment by enhancing microvascular permeability allowing the movement of leukocytes through the vascular endothelium and into tissues. Fourth, LTs contribute to effector T cell recruitment and dendritic cell trafficking following antigen stimulation and may play an essential role in directing the adaptive immune response [119–123]. Finally, LTB_4 may effectively enhance the number of leukocytes at a focus of infection by delaying leukocyte apoptosis [124, 125].

In addition to leukocyte recruitment, the LTs contribute to host defense by augmenting the ability of macrophages and neutrophils to phagocytose microorganisms. Culturing macrophages with exogenous LTB_4 or LTC_4 enhances phagocytosis of *Trypanosoma cruzi* [126, 127], *Salmonella typhimurium* (LTB_4 only) [128], and *Klebsiella pneumoniae* [107]. Conversely, inhibiting LT synthesis reduces phagocytosis of bacteria [107] as well as opsonized particles (Fig. 2). Pharmacological inhibition of LT synthesis reduced both the percent of macrophages that had captured

beads and the number of beads per macrophage, which has been quantitated as a 50% decrease in phagocytic index [107]. This effect of LT inhibition on phagocytosis is completely reversed by the concomitant addition of LTs and can be mimicked by selective LT receptor blockers [107].

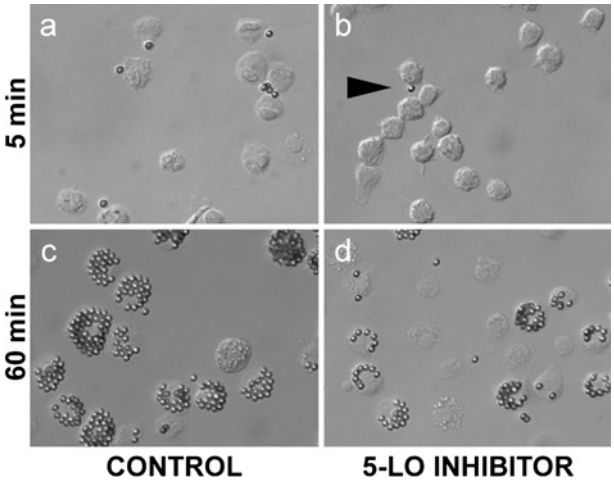

Figure 2. The effect of the 5-LO inhibitor AA-861 on phagocytosis of IgG-opsonized beads by rat alveolar macrophages. Macrophages (2×10^5/well) were untreated (*a*, *c*) or pretreated with AA-861 (10 μM) for 20 min (*b*, *d*) before addition of beads. After 5- or 60-min challenge, wells were washed to remove free beads, fixed with 4% paraformaldehyde and imaged. Arrowhead in (*b*) indicates lone bead in field.

The means by which the LTs facilitate phagocytosis include the enhancement of opsonin (FcγR) receptor- and complement (CR) receptor-mediated phagocytosis. For instance, phagocytosis of IgG-opsonized targets is increased with both LTB_4 and cysLTs [129, 130]. LTB_4 enhances phagocytosis of IgG-opsonized targets by enhancing the activation of the tyrosine kinase, syk, during ligation of the Fcγ receptor [131]. In addition, LTB_4, but not the cysLTs, can also enhance CR-mediated phagocytosis in neutrophils by enhancing binding of complement opsonized targets due to the increased expression of the CR3 receptor [130, 132].

A role for LTs in microbial killing has been demonstrated in a number of animal models of infectious disease and in monocytes, macrophages, and neutrophils cultured *in vitro* [96]. Using 5-$LO^{-/-}$ mice, Bailie et al. [97] demonstrated that alveolar macrophages (AMs) from 5-$LO^{-/-}$ mice exhibit an impaired ability to kill *K. pneumoniae in vitro.* Subsequent studies revealed that the impairment in the killing of bacteria in AMs from 5-$LO^{-/-}$ mice could be reconstituted with the addition of exogenous LTB_4 and that the provision of LTB_4 or cysLTs to AMs from normal animals augments bacterial killing *in vitro* [133]. Others have also demonstrated that the exogenous administration of LTB_4 or LTC_4 to macrophages enhances killing of many different types of microorganisms, including *Trypanosoma cruzi* [126, 127, 134], *Pseudomonas aeruginosa* and *Salmonella typhimurium* (LTB_4 only) [128], *Toxoplasma gondii* [135], and *Leishmania amazonensis* [105]. In addition, the exogenous administration of LTB_4, the most abundantly produced 5-LO product in neutrophils, enhances neutrophil-mediated killing of *Mycobacterium bovis* [113], *Cryptococcus neoformans* [136], and *Schistosoma mansoni* [137]. The mechanisms by which LTs enhance microbial killing include the augmentation of leukocyte antimicrobial functions. For example, LTB_4 increases lysosomal enzyme release [138], induces nitric oxide synthesis [105, 134], enhances the release of α-defensins from neutrophils [139], and augments reactive oxygen intermediate production in macrophages by activating the assembly of proteins that form the NADPH oxidase complex [133, 140, 141]. Exogenous cysLTs also possess antimicrobial properties, since they induce nitric oxide generation from neutrophils [141] and activate the production of reactive oxygen intermediates in macrophages [133]. Finally, the LTs also indirectly enhance host defense by inducing gene expression. For example, LTs increase the synthesis of other proinflammatory mediators that augment host defense mechanisms. These effects on gene expression, and others, are of growing interest.

LTs modulate gene expression: Deciphering the good and the bad roles

The diversity of roles for LTB_4 and cysLTs in disease suggest that these mediators have a variety of effects. For example, the different LTs promote the generation of soluble pro-inflammatory mediators. One mechanism is the triggered release of preformed mediators (*e.g.*, cysLT-mediated release of IL-4 in human eosinophils [142, 143], LTB_4-induced release of α-defensins [139] and the anti-microbial peptide LL-37 [144]). Another important action of LTs is through induced gene expression of soluble intercellular messengers (*e.g.*, IL-6 [145, 146], IL-8 [147]) and/or the enzymes involved in the biosynthesis of pro-inflammatory mediators (*e.g.*, COX-2 [148]). In fact, LTB_4 and CysLTs have been shown to induce many other soluble mediators of inflammation *ex vivo* (Tables 1 and 2) by cellular mechanisms that are, as yet, poorly defined. These roles for LTs may be positive, in that they drive important components of host defense. Of course, the persistent over-production of pro-inflammatory mediators would be less desirable.

Table 1. Up-regulation of gene expression by LTB_4 *ex vivo*.

Gene	Cell type	Co-stimulus	Receptor	Signaling	Ref.
BLT_1	HUVEC	LPS	BLT_1		[153]
CCR7	Mouse dendritic cells	–	–		[149]
CD11b	Human monocytes	–	–		[154]
CD11c	Human monocytes	–	–		[154]
CD18	Human monocytes	–	–		[154]
CD23	B-CLL	–	–		[155]
	Human monocytes	IL-4	–		[156, 157]
CD54	B-CLL	CD40L	–		[155]
CD150	B-CLL	CD40L	–		[155]
	Mouse splenocytes	Con A	–		[158]
c-fos[a], c-jun[a]	Human monocytes	–	–		[152, 159]
IFN-γ	Mouse lymphocytes	–	–		[160]
IgE	Human PBMC	IL-4	–		[157]
IL-2	Mouse lymphocytes	–	–		[161]
	Mouse splenocytes	Con A	–		[158]
IL-2Rβ	Human lymphocytes	–	–		[162]
	Human monocytes	–	–		[163]
IL-4	Mouse splenocytes	Con A	–		[158]
	Human lymphocytes	–	–		[160]
IL-5	Human lymphocytes	–	–		[164]
IL-6	Human monocytes	–	–	NF-chi B, NF-IL6,	[145, 146]
IL-8	Human dendritic cells	–	–		[147]
	Human neutrophils	Fibrinogen	–	Gαi	[165]
	16HBEC	–	–	NF-κB	[166]
IL-10	Mouse splenocytes	Con A	–		[158]
iNOS	Mouse peritoneal macrophages	–	–		[105]
MCP-1	Human monocytes	–	BLT_1	ERK, JNK, NF-κB	[167]
	HUVEC	LPS	BLT_1		[153]
MIP-1β	Human neutrophils	–	–		[165]
TNF-α	Human monocytes	IL-2	–		[163]

[a] Only investigated at the mRNA level.
HUVEC, human umbilical vascular endothelial cells; B-CLL, B cell chronic lymphoid leukemia cells; PBMC, peripheral blood mononuclear cells; HBEC, human bronchial epithelial cells.

Although the LT receptors are differentially expressed and regulated, they may also act in a redundant manner and promote the expression of similar gene products. For example, LTB_4 has recently been shown to activate dendritic cells and increase their surface expression of the chemokine receptor CCR7 and their response to the specific CCR7 ligand CCL19 [149]. Interestingly, a similar increase of CCL19 sensitivity data was also observed when dendritic cells were activated with LTC_4, indicating that CysLTs are likely to up-regulate CCR7 as well [150]. Similar redundancy was also observed between CysLTs and thrombin in activated endothelial cells, although the induction of some transcription factors was unique to CysLTs [80]. Redundancy is a hallmark of essential biological systems, serving the same role as an understudy in a stage performance.

In some cases, LTs serve to amplify gene expression that is driven by a co-stimulus. For example, LTC_4 and LTD_4 increased MMP-9 mRNA expression induced by TNF-α, and the $CysLT_1$ inhibitor pranlukast completely inhibited this enhancement [151]. However, many of the effects of LTs on gene expression did not require a co-stimulus. Interestingly, LTD_4, acting through $CysLT_2$, induces several transcription factors, including c-fos and c-jun [147, 152], as well as members of the early growth response (egr) and the nuclear receptor subfamily group A (NR4A) families [80]. As a result, these changes may alter signaling by other mediators.

Table 2. Up-regulation of gene expression by cysLTs *ex vivo*.

Gene	Cell type	Co-stimulus	Receptor	Signaling	Ref.
Aquaporin 4	Rat astrocytes	–	$CysLT_2$		[168]
***c-fos*[a], *c-jun*[a]**	HEK-293L1[b]	–	$CysLT_1$	NF-κB, AP-1	[147]
COX-2	HUVEC	–	$CysLT_2$	PLC, NFAT	[148]
$cPLA_2\alpha$	Int 407[c] Caco-2[d]	– –	– –	Gαi, p38, MEK-1, PKC	[169]
$CysLT_1$[a]	Murine tracheal epithelial cells	–	–		[170]
$CysLT_2$[a]	Murine tracheal epithelial cells Rat astrocytes	– –	–		[170] [168]
Egr-1	HUVEC	–	$CysLT_2$		[80, 81]
Egr-2	HUVEC	–	$CysLT_2$		[80, 81]
Egr-3	HUVEC	–	$CysLT_2$	PLCβ	[80, 81]
IgE	Human B lymphocytes	CD40L	$CysLT_1$		[171]
IL-5	Human mast cells	–	$CysLT_1$	ERK, NFAT, p38	[172, 173]
IL-8	THP-1[e] HEK-293L1 HUVEC Human mast cells	– – – –	$CysLT_1$ $CysLT_1$ $CysLT_2$ $CysLT_2$	 NF-κB, AP-1 Gαi, p38	[147] [147] [80] [173]
IL-10	Mouse BMDC	*D. farinae*			[174]
IL-11	Murine tracheal epithelial cells	–	$CysLT_1$		[170]
MIP-1α	Rat alveolar macrophages	LPS	$CysLT_1$		[175]
MIP-1β	Human mast cells	–	$CysLT_2$	ERK, NFAT	[176]
MMP-9	THP-1, human monocytes	TNF-α	$CysLT_1$		[151]
NR4A1 [a]	HUVEC	–	$CysLT_2$		[80]
NR4A2 [a]	HUVEC	–	$CysLT_2$		[80]
NR4A3 [a]	HUVEC	–	$CysLT_2$		[80]
PCKα [a]	αT3–1[f]	–	–		[177]
PKCβ [a]	αT3–1	–	–		[177]
RANTES	Mouse lung mononuclear cells	–	–	NF-κB	[178]
Tissue factor	HUVEC	–	$CysLT_2$		[80]
TGF-β1	Human airway epithelial cells	–	$CysLT_1$	p38, ATF-2	[179]
TNF-α	Human mast cells Rat alveolar macrophages	– LPS	$CysLT_1$ $CysLT_1$	ERK, NFAT	[176] [175]

[a] Only investigated at the mRNA level.
[b] Human Embryonic Kidney Cells Stably transfected with the $CysLT_1$.
[c] Human embryonic intestinal cells.
[d] Human colon adenocarcinoma cells.
[e] Human acute monocytic leukemia cells.
[f] Pituitary gonadotroph cells.
BMDC, bone marrow-derived dendritic cells.

Summary

The best-known roles for LTB_4 and the cysLTs are in asthma, allergic responses and inflammatory diseases. Current research also places LTs in major pathologies, including various cancers and cardiovascular diseases. However, numerous studies also indicate that LTs play critical, positive roles in host defense against bacterial, fungal and viral infections. With the development of novel approaches to suppress LT synthesis and action, these positive roles must be kept in mind.

Acknowledgements. Generous support for this review was provided by a Canadian Institutes of Health Research Fellowship (N.F.) and by National Institutes of Health grants HL077417 (P.M.) and AI43955 (T.G.B.).

1 Hirata, K., Maghni, K., Borgeat, P. and Sirois, P. (1990) Guinea pig alveolar eosinophils and macrophages produce leukotriene B_4 but no peptidoleukotrienes. J. Immunol. 144, 1880 – 1885.
2 Henderson, R. F., Leung, H. W., Harmsen, A. G. and McClellan, R. O. (1988) Species differences in release of arachidonate metabolites in response to inhaled diluted diesel exhaust. Toxicol. Lett. 42, 325 – 332.

3 Yokomizo, T., Izumi, T., Chang, K., Takuwa, Y. and Shimizu, T. (1997) A G-protein-coupled receptor for leukotriene B_4 that mediates chemotaxis. Nature 387, 620 – 624.

4 Gaudreau, R., Le Gouill, C., Metaoui, S., Lemire, S., Stankova, J. and Rola-Pleszczynski, M. (1998) Signalling through the leukotriene B_4 receptor involves both α_i and α_{16}, but not α_q or α_{11} G-protein subunits. Biochem. J. 335, 15 – 18.

5 Yokomizo, T., Kato, K., Terawaki, K., Izumi, T. and Shimizu, T. (2000) A second leukotriene B(4) receptor, BLT2. A new therapeutic target in inflammation and immunological disorders. J. Exp. Med. 192, 421 – 432.

6 Lin, Q., Ruuska, S. E., Shaw, N. S., Dong, D. and Noy, N. (1999) Ligand selectivity of the peroxisome proliferator-activated receptor alpha. Biochemistry 38, 185 – 190.

7 Devchand, P. R., Keller, H., Peters, J. M., Vazquez, M., Gonzalez, F. J. and Wahli, W. (1996) The PPARα-leukotriene B_4 pathway to inflammation control. Nature 384, 39 – 43.

8 Lynch, K. R., O'Neil, G. P., Liu, Q., Im, D. S., Sawyer, N., Metters, K. M., Coulombe, N., Abramovitz, M., Figueroa, D. J., Zeng, Z., Connolly, B. M., Bai, C., et al. (1999) Characterization of the human cysteinyl leukotriene CysLT1 receptor. Nature 399, 789 – 793.

9 Heise, C. E., O'Dowd, B. F., Figueroa, D. J., Sawyer, N., Nguyen, T., Im, D., Stocco, R., Bellefeuille, J. N., Abramovitz, M., Cheng, R., Williams, D. L., Zeng, Z. et al. (2000) Characterization of the human cysteinyl leukotriene 2 receptor. J. Biol. Chem. 275, 30531 – 30536.

10 Ciana, P., Fumagalli, M., Trincavelli, M. L., Verderio, C., Rosa, P., Lecca, D., Ferrario, S., Parravicini, C., Capra, V., Gelosa, P., Guerrini, U., Belcredito, S. et al. (2006) The orphan receptor GPR17 identified as a new dual uracil nucleotides/cysteinyl-leukotrienes receptor. EMBO J. 25, 4615 – 4627.

11 Gimbrone, M. A., Brock, A. F. and Schafer, A. I. (1984) Leukotriene B_4 stimulates polymorphonuclear leukocyte adhesion to cultured vascular endothelial cells. J. Clin. Invest. 74, 1552 – 1555.

12 Ford-Hutchinson, A. W., Bray, M. A., Doig, M. V., Shipley, M. E. and Smith, M. J. H. (1980) Leukotriene B_4, a potent chemokinetic and aggregating substance released from polymorphonuclear leukocytes. Nature 286, 264 – 265.

13 Claesson, H. E. and Feinmark, S. J. (1984) Relationship of cyclic-AMP levels in leukotriene B_4-stimulated leukocytes to lysosomal enzyme release and the generation of superoxide anions. Biochim. Biophys. Acta 804, 52 – 57.

14 Cunningham, F. M., Shipley, M. E. and Smith, M. J. (1980) Aggregation of rat polymorphonuclear leucocytes *in vitro*. J. Pharm. Pharmacol. 32, 377 – 380.

15 Lauritsen, K., Laursen, L. S., Bukhave, K. and Rask-Madsen, J. (1986) Effects of topical 5-aminosalicylic acid and prednisolone on prostaglandin E_2 and leukotriene B_4 levels determined by equilibrium *in vivo* dialysis of rectum in relapsing ulcerative colitis. Gastroenterology 91, 837 – 844.

16 Cole, A. T., Pilkington, B. J., McLaughlan, J., Smith, C., Balsitis, M. and Hawkey, C. J. (1996) Mucosal factors inducing neutrophil movement in ulcerative colitis: the role of interleukin 8 and leukotriene B_4. Gut. 39, 248 – 254.

17 Sharon, P. and Stenson, W. F. (1984) Enhanced synthesis of leukotriene B_4 by colonic mucosa in inflammatory bowel disease. Gastroenterology 86, 453 – 460.

18 Griffiths, R. J., Pettipher, E. R., Koch, K., Farrell, C. A., Breslow, R., Conklyn, M. J., Smith, M. A., Hackman, B. C., Wimberely, D. J., Milici, A. J., Scampoli, D. N., Cheng, J. B. et al. (1995) Leukotriene B_4 plays a critical role in the progression of collagen-induced arthritis. Proc. Natl. Acad. Sci. USA 92, 517 – 521.

19 Klickstein, L. B., Shapleigh, C. and Goetzl, E. J. (1980) Lipoxygenation of arachidonic acid as a source of polymorphonuclear leukocyte chemotactic factors in synovial fluid and tissue in rheumatoid arthritis and spondyloarthritis. J. Clin. Invest. 66, 1166 – 1170.

20 Ruzicka, T., Simmet, T., Peskar, B. A. and Ring, J. (1986) Skin levels of arachidonic acid-derived inflammatory mediators and histamine in atopic dermatitis and psoriasis. J. Invest. Dermatol. 86, 105 – 108.

21 Cromwell, W., Walport, M., Taylor, G. W., Morris, H. R., O'Driscoll, B. R. and Kay, A. B. (1981) Identification of leukotrienes D and B in sputum from cystic fibrosis patients. Lancet 2, 164 – 165.

22 Dahlen, S. E., Hedqvist, P., Hammarstrom, S. and Samuelsson, B. (1980) Leukotrienes are potent constrictors of human bronchi. Nature 288, 484 – 486.

23 Shelhamer, J., Marom, Z., Sun, F., Bach, M. and Kaliner, M. (1982) The effects of arachinoids and leukotrienes on the release of mucus from human airways. Chest 81, 36 – 37.

24 Michelassi, F., Landa, L., Hill, R., Lowenstein, E., Watkins, W., Petkau, A. and Zapol, W. M. (1982) Leukotriene D_4: a potent coronary artery vasoconstrictor associated with impaired ventricular contraction. Science 217, 841 – 843.

25 Schellenberg, R. R. and Foster, A. (1984) Differential activity of leukotrienes upon human pulmonary vein and artery. Prostaglandins 27, 475 – 482.

26 Drazen, J. M., Austen, K. F., Lewis, R. A., Clark, D. A., Goto, G., Marfat, A. and Corey, E. J. (1980) Comparative airway and vascular activity of leukotrienes C-1 and D *in vivo* and *in vitro*. Proc. Natl. Acad. Sci. USA 77, 4354 – 4358.

27 Dahlen, S. E., Bjork, J., Hedqvist, P., Arfors, K. E., Hammarstrom, S., Lindgren, J. A. and Samuelsson, B. (1981) Leukotrienes promote plasma leakage and leukocyte adhesion in postcapillary venules: *in vivo* effects with relevance to the acute inflammatory response. Proc. Natl. Acad. Sci. USA 78, 3887 – 3891.

28 Neufeld, E. J., Majerus, P. W., Krueger, C. M. and Saffitz, J. E. (1985) Uptake and subcellular distribution of [^{3}H]arachidonic acid in murine fibrosarcoma cells measured by electron microscope autoradiography. J. Cell Biol. 101, 573 – 581.

29 Luo, M., Jones, S. M., Peters-Golden, M. and Brock, T. G. (2003) Nuclear localization of 5-lipoxygenase as a determinant of leukotriene B_4 synthetic capacity. Proc. Natl. Acad. Sci. USA 100, 12165 – 12170.

30 Bonventre, J. V., Huang, Z., Taheri, M. R., O'Leary, E., Li, E., Moskowitz, M. A. and Sapirstein, A. (1997) Reduced fertility and postischaemic brain injury in mice deficient in cytosolic phospholipase A_2. Nature 390, 622 – 625.

31 Svensson, U., Houweling, M., Holst, E. and Sundler, R. (1993) Phosphorylation and activation of the arachidonate-mobilizing phospholipase A_2 in macrophages in response to bacteria. Eur. J. Biochem. 213, 81 – 86.

32 Xu, X., Rock, C., Qiu, Z., Leslie, C. and Jackowski, S. (1994) Regulation of cytosolic phospholipase A_2 phosphorylation and eicosanoid production by colony-stimulating factor 1. J. Biol. Chem. 269, 31693 – 31700.

33 Kramer, R., Roberts, E., Manetta, J., Hyslop, P. and Jakubowski, J. (1993) Thrombin-induced phosphorylation and activation of Ca^{2+}-sensitive cytosolic phospholipase A_2 in human platelets. J. Biol. Chem. 268, 26795 – 26804.

34 Bolognese, B., McCord, M. and Marshall, L. (1995) Differential regulation of elicited-peritoneal macrophage 14 kDa and 85 kDa phospholipase A_2(s) by transforming growth factor-beta. Biochim. Biophys. Acta 1256, 201 – 209.

35 Brock, T. G., McNish, R. W., Coffey, M. J., Ojo, T. C., Phare, S. M. and Peters-Golden, M. (1996) Effect of granulocyte-macrophage colony-stimulating factor on eicosanoid production by mononuclear phagocytes. J. Immunol. 156, 2522 – 2527.

36 Nakamura, T., Lin, L., Kharbanda, S., Knopf, J. and Kufe, D. (1992) Macrophage colony stimulating factor activates phosphatidylcholine hydrolysis by cytoplasmic phospholipase A_2. EMBO J. 11, 4917 – 4922.

37 Mancuso, P., Canetti, C., Gottschalk, A., Tithof, P. K. and Peters-Golden, M. (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. Lung Cell. Mol. Physiol. 287, L497 – 502.
38 Munoz, N. M., Kim, Y. J., Meliton, A. Y., Kim, K. P., Han, S. K., Boetticher, E., O'Leary, E., Myou, S., Zhu, X., Bonventre, J. V., Leff, A. R. and Cho, W. (2003) Human group V phospholipase A_2 induces group IVA phospholipase A_2-independent cysteinyl leukotriene synthesis in human eosinophils. J. Biol. Chem. 278, 38813 – 38820.
39 Hidi, R., Vargaftig, B. and Touqui, L. (1993) Increased synthesis and secretion of a 14-kDa phospholipase A_2 by guinea pig alveolar macrophages. J. Immunol. 151, 5613 – 5623.
40 Lyons-Giordano, B., Davis, G., Galbraith, W., Pratta, M. and Arner, E. (1989) Interleukin-1β stimulates phospholipase A_2 mRNA synthesis in rabbit articular chondrocytes. Biochem. Biophys. Res. Commun. 164, 488 – 495.
41 Folco, G. and Murphy, R. C. (2006) Eicosanoid transcellular biosynthesis: from cell-cell interactions to *in vivo* tissue responses. Pharmacol. Rev. 58, 375 – 388.
42 Needleman, P., Turk, J., Jakschik, B. A., Morrison, A. R. and Lefkowith, J. B. (1986) Arachidonic acid metabolism. Annu. Rev. Biochem. 55, 69 – 102.
43 Samuelsson, B. and Funk, C. D. (1989) Enzymes involved in the biosynthesis of leukotriene B_4. J. Biol. Chem. 264, 19469 – 19472.
44 Radmark, O. and Samuelsson, B. (2005) Regulation of 5-lipoxygenase enzyme activity. Biochem. Biophys. Res. Commun. 338, 102 – 110.
45 Luo, M., Flamand, N. and Brock, T. G. (2006) Metabolism of arachidonic acid to eicosanoids within the nucleus. Biochim. Biophys. Acta 1761, 618 – 625.
46 Dahlen, B., Kumlin, M., Johansson, H., Larsson, C., Zetterstrom, O., Granstrom, E. and Dahlen, S. E. (1991) Aspirin-sensitive asthmatics have elevated basal levels of leukotriene E_4 in the urine, and bronchial provocation with lysine-aspirin results in further release. Am. Rev. Respir. Dis. 143, 599.
47 Wilborn, J., Bailie, M., Coffey, M., Burdick, M., Strieter, R. and Peters-Golden, M. (1996) Constitutive activation of 5-lipoxygenase in the lungs of patients with idiopathic pulmonary fibrosis. J. Clin. Invest. 97, 1827 – 1836.
48 Moody, T. W., Leyton, J., Martínez, A., Hong, S., Malkinson, A. and Mulshine, J. L. (1998) Lipoxygenase inhibitors prevent lung carcinogenesis and inhibit non-small cell lung cancer growth. Exp. Lung Res. 24, 617 – 628.
49 Avis, I. M., Jett, M., Boyle, T., Vos, M. D., Moody, T., Treston, A. M., Martínez, A. and Mulshine, J. L. (1996) Growth control of lung cancer by interruption of 5-lipoxygenase-mediated growth factor signaling. J. Clin. Invest. 97, 806 – 813.
50 Hennig, R., Ding, X. Z., Tong, W. G., Schneider, M. B., Standop, J., Friess, H., Buchler, M. W., Pour, P. M. and Adrian, T. E. (2002) 5-Lipoxygenase and leukotriene B_4 receptor are expressed in human pancreatic cancers but not in pancreatic ducts in normal tissue. Am. J. Pathol. 161, 421 – 428.
51 Yoshimura, R., Matsuyama, M., Tsuchida, K., Kawahito, Y., Sano, H and Nakatani, T. (2003) Expression of lipoxygenase in human bladder carcinoma and growth inhibition by its inhibitors. J. Urol. 170, 1994 – 1999.
52 Ghosh, J. (2003) Inhibition of arachidonate 5-lipoxygenase triggers prostate cancer cell death through rapid activation of c-Jun N-terminal kinase. Biochem. Biophys. Res. Commun. 307, 342 – 349.
53 Matsuyama, M., Yoshimura, R., Mitsuhashi, M., Tsuchida, K., Takemoto, Y., Kawahito, Y., Sano, H. and Nakatani, T. (2005) 5-Lipoxygenase inhibitors attenuate growth of human renal cell carcinoma and induce apoptosis through arachidonic acid pathway. Oncol. Rep. 14, 73 – 79.
54 Hoque, A., Lippman, S. M., Wu, T. T., Xu, Y., Liang, Z. D., Swisher, S., Zhang, H., Cao, L., Ajani, J. A. and Xu, X. C. (2005) Increased 5-lipoxygenase expression and induction of apoptosis by its inhibitors in esophageal cancer: a potential target for prevention. Carcinogenesis 26, 785 – 791.
55 Soumaoro, L. T., Iida, S., Uetake, H., Ishiguro, M., Takagi, Y., Higuchi, T., Yasuno, M., Enomoto, M. and Sugihara, K. (2006) Expression of 5-lipoxygenase in human colorectal cancer. World J. Gastroenterol. 12, 6355 – 6360.
56 Chen, X., Sheller, J., Johnson, E. and Funk, C. (1994) Role of leukotrienes revealed by targeted disruption of the 5-lipoxygenase gene. Nature 372, 179 – 182.
57 Goulet, J., Snouwaert, J., Latour, A., Coffman, T. and Koller, B. (1994) Altered inflammatory responses in leukotriene-deficient mice. Proc. Natl. Acad. Sci. USA 91, 12852 – 12856.
58 Byrum, R. S., Goulet, J. L., Griffiths, R. J. and Koller, B. H. (1997) Role of the 5-lipoxygenase-activating protein (FLAP) in murine acute inflammatory responses. J. Exp. Med. 185, 1065 – 1075.
59 Griffiths, R. J., Smith, M. A., Roach, M. L., Stock, J. L., Stam, E. J., Milici, A. J., Scampoli, D. N., Eskra, J. D., Byrum, R. S., Koller, B. H. and McNeish, J. D. (1997) Collagen-induced arthritis is reduced in 5-lipoxygenase-activating protein-deficient mice. J. Exp. Med. 185, 1123 – 1129.
60 Chen, M., Lam, B. K., Kanaoka, Y., Nigrovic, P. A., Audoly, L. P., Austen, K. F. and Lee, D. M. (2006) Neutrophil-derived leukotriene B_4 is required for inflammatory arthritis. J. Exp. Med. 203, 837 – 842.
61 Shim, Y. M., Zhu, Z., Zheng, T., Lee, C. G., Homer, R. J., Ma, B. and Elias, J. A. (2006) Role of 5-lipoxygenase in IL-13-induced pulmonary inflammation and remodeling. J. Immunol. 177, 1918 – 1924.
62 Cuzzocrea, S., Rossi, A., Serraino, I., Di Paola, R., Dugo, L., Genovese, T., Britti, D., Sciarra, G., De Sarro, A., Caputi, A. and Sautebin, L. (2003) 5-Lipoxygenase knockout mice exhibit a resistance to acute pancreatitis induced by cerulein. Immunology 110, 120 – 130.
63 Voelkel, N. F., Tuder, R. M., Wade, K., Hoper, M., Lepley, R. A., Goulet, J. L., Koller, B. H. and Fitzpatrick, F. (1996) Inhibition of 5-lipoxygenase-activating protein (FLAP) reduces pulmonary vascular reactivity and pulmonary hypertension in hypoxic rats. J. Clin. Invest. 97, 2491 – 2498.
64 Irvin, C. G., Tu, U. P., Sheller, J. R. and Funk, C. D. (1997) 5-Lipoxygenase products are necessary for ovalbumin-induced airway responsiveness in mice. Am. J. Physiol. 272, L1053-L1058.
65 Goulet, J. L., Griffiths, R. C., Ruiz, P., Spurney, R. F., Pisetsky, D. S., Koller, B. H. and Coffman, T. M. (1999) Deficiency of 5-lipoxygenase abolishes sex-related survival differences in MRL-lpr/lpr mice. J. Immunol. 163, 359 – 366.
66 Goulet, J. L., Griffiths, R. C., Ruiz, P., Mannon, R. B., Flannery, P., Platt, J. L., Koller, B. H. and Coffman, T. M. (2001) Deficiency of 5-lipoxygenase accelerates renal allograft rejection in mice. J. Immunol. 167, 6631 – 6636.
67 Peters-Golden, M., Bailie, M., Marshall, T., Wilke, C., Phan, S. H., Toews, G. B. and Moore, B. B. (2002) Protection from pulmonary fibrosis in leukotriene-deficient mice. Am. J. Respir. Crit. Care Med. 165, 229 – 235.
68 Cuzzocrea, S., Rossi, A., Serraino, I., Di Paolo, R., Dugo, L., Genovese, T., Caputi, A. and Sautebin, L. (2003) 5-Lipoxygenase knockout mice exhibit a resistance to splanchnic artery occlusion shock. Shock 20, 230 – 236.
69 Patel, N., Cuzzocrea, S., Chatterjee, P., Di Paola, R., Sautebin, L., Britti, D. and Thiemermann, C. (2004) Reduction of renal ischemia-reperfusion injury in 5-lipoxygenase knockout mice and by the 5-lipoxygenase inhibitor zileuton. Mol. Pharmacol. 66, 220 – 227.
70 Byrum, R. S., Goulet, J. L., Snouwaert, J. N., Griffiths, R. J. and Koller, B. H. (1999) Determination of the contribution of cysteinyl leukotrienes and leukotriene B_4 in acute inflammatory responses using 5-lipoxygenase- and leukotriene A_4 hydrolase-deficient mice. J. Immunol. 163, 6810 – 6819.
71 Kim, N. D., Richard, C. C., Seung, E., Tager, A. M. and Luster, A. D. (2006) A unique requirement for the leukotriene B_4 receptor BLT1 for neutrophil recruitment in inflammatory arthritis. J. Exp. Med. 203, 829 – 835.

72 Shao, W. H., Del Prete, A., Bock, C. B. and Haribabu, B. (2006) Targeted disruption of leukotriene B_4 receptors BLT1 and BLT2: a critical role for BLT1 in collagen-induced arthritis in mice. J. Immunol. 176, 6254 – 6261.

73 Beller, T. C., Friend, D. S., Maekawa, A., Lam, B. K., Austen, K. F. and Kanaoka, Y. (2004) Cysteinyl leukotriene 1 receptor controls the severity of chronic pulmonary inflammation and fibrosis. Proc. Natl. Acad. Sci. USA 101, 3047 – 3052.

74 Beller, T. C., Maekawa, A., Friend, D. S., Austen, K. F. and Kanaoka, Y. (2004) Targeted gene disruption reveals the role of the cysteinyl leukotriene 2 receptor in increased vascular permeability and in bleomycin-induced pulmonary fibrosis in mice. J. Biol. Chem. 279, 46129 – 46134.

75 Mehrabian, M., Allayee, H., Wong, J., Shih, W., Wang, X. P., Shaposhnik, Z., Funk, C. D. and Lusis, A. J. (2002) Identification of 5-lipoxygenase as a major gene contributing to atherosclerosis susceptibility in mice. Circ. Res. 91, 120 – 126.

76 Spanbroek, R., Grabner, R., Lotzer, K., Hildner, M., Urbach, A., Ruhling, K., Moos, M. P., Kaiser, B., Cohnert, T. U., Wahlers, T., Zieske, A., Plenz, G. et al. (2003) Expanding expression of the 5-lipoxygenase pathway within the arterial wall during human atherogenesis. Proc. Natl. Acad. Sci. USA 100, 1238 – 1243.

77 Heller, E. A., Liu, E., Tager, A. M., Sinha, S., Roberts, J. D., Koehn, S. L., Libby, P., Aikawa, E. R., Chen, J. Q., Huang, P., Freeman, M. W., Moore, K. J. et al. (2005) Inhibition of atherogenesis in BLT1-deficient mice reveals a role for LT B_4 and BLT1 in smooth muscle cell recruitment. Circulation 112, 578 – 586.

78 Back, M., Bu, D. X., Branstrom, R., Sheikine, Y., Yan, Z. Q. and Hansson, G. K. (2005) Leukotriene B_4 signaling through NF-κB-dependent BLT1 receptors on vascular smooth muscle cells in atherosclerosis and intimal hyperplasia. Proc. Natl. Acad. Sci. USA 102, 17501 – 17506.

79 Qiu, H., Gabrielsen, A., Agardh, H. E., Wan, M., Wetterholm, A., Wong, C. H., Hedin, U., Swedenborg, J., Hansson, G. K., Samuelsson, B., Paulsson-Berne, G. and Haeggstrom, J. Z. (2005) Expression of 5-lipoxygenase and leukotriene A_4 hydrolase in human atherosclerotic lesions correlates with symptoms of plaque instability. Proc. Natl. Acad. Sci. USA 103, 8161 – 8166.

80 Uzonyi, B., Lotzer, K., Jahn, S., Kramer, C., Hildner, M., Bretschneider, E., Radke, D., Beer, M., Vollandt, R., Evans, J. F., Funk, C. D. and Habenicht, A. J. (2006) Cysteinyl leukotriene 2 receptor and protease-activated receptor 1 activate strongly correlated early genes in human endothelial cells. Proc. Natl. Acad. Sci. USA 103, 6326 – 6331.

81 Woszczek, G., Chen, L., Nagineni, S., Alsaaty, S., Harry, A., Logun, C., Pawliczak, R. and Shelhamer, J. H. (2007) IFN-γ induces cysteinyl leukotriene receptor 2 expression and enhances the responsiveness of human endothelial cells to cysteinyl leukotrienes. J. Immunol. 178, 5262 – 5270.

82 Funk, C. D. (2005) Leukotriene modifiers as potential therapeutics for cardiovascular disease. Nat. Rev. Drug Discov. 4, 664 – 682.

83 Lotzer, K., Funk, C. D. and Habenicht, A. J. (2005) The 5-lipoxygenase pathway in arterial wall biology and atherosclerosis. Biochim. Biophys. Acta 1736, 30 – 37.

84 Radmark, O. and Samuelsson, B. (2007) 5-Lipoxygenase: Regulation and possible involvement in atherosclerosis. Prostaglandins Other Lipid Mediat. 83, 162 – 174.

85 Skerrett, S. J., Henderson, W. R. and Martin, T. R. (1990) Alveolar macrophage function in rats with severe protein calorie malnutrition: arachidonic acid metabolism, cytokine release, and antimicrobial activity. J. Immunol. 144, 1052 – 1061.

86 Cederholm, T., Lindgren, J. and Palmblad, J. (2000) Impaired leukotriene C_4 generation in granulocytes from protein-energy malnourished chronically ill elderly. J. Intern. Med. 247, 715 – 722.

87 Anstead, G. M., Chandrasekar, B., Zhang, Q. and Melby, P. C. (2003) Multinutrient undernutrition dysregulates the resident macrophage proinflammatory cytokine network, nuclear factor-κB activation, and nitric oxide production. J. Leukoc. Biol. 74, 982 – 992.

88 Mancuso, P., Huffnagle, G. B., Olszewski, M. A., Phipps, J. and Peters-Golden, M. (2006) Leptin corrects host defense defects following acute starvation in murine pneumococcal pneumonia. Am. J. Respir. Crit. Care Med. 173, 212 – 218.

89 Laviolette, M., Coulombe, R., Picard, S., Braquet, P. and Borgeat, P. (1986) Decreased leukotriene B_4 synthesis in smokers' alveolar macrophages *in vitro*. J. Clin. Invest. 77, 54 – 60.

90 Balter, M. S., Toews, G. B. and Peters-Golden, M. (1989) Multiple defects in arachidonate metabolism in alveolar macrophages from young asymptomatic smokers. J. Lab. Clin. Med. 114, 662 – 673.

91 Coffey, M. J., Wilcoxen, S. E., Phare, S. M., Simpson, R. U., Gyetko, M. R. and Peters-Golden, M. (1994) Reduced 5-lipoxygenase metabolism of arachidonic acid in macrophages from 1,25-dihydroxyvitamin D3-deficient rats. Prostaglandins 48, 313 – 329.

92 Coffey, M., Phare, S. M., Kazanjian, P. H. and Peters-Golden, M. (1996) 5-Lipoxygenase metabolism in alveolar macrophages from subjects infected with the human immunodeficiency virus. J. Immunol. 157, 393 – 399.

93 Mayatepek, E., Flock, B., Zelezny, R., Kreutzer, K. and von Giesen, H. J. (1999) LTB_4 and LTC_4 are absent in the cerebrospinal fluid of human immunodeficiency virus type 1-seropositive persons with toxoplasmic encephalitis: evidence for inhibition of 5-lipoxygenase by *Toxoplasma gondii*. J. Infect. Dis. 179, 714 – 716.

94 Claria, J., Titos, E., Jimenez, W., Ros, J., Gines, P., Arroyo, V., Rivera, F. and Rodes, J. (1998) Altered biosynthesis of leukotrienes and lipoxins and host defense disorders in patients with cirrhosis and ascites. Gastroenterology 115, 147 – 156.

95 Jubiz, W., Draper, R. E., Gale, J. and Nolan, G. (1984) Decreased leukotriene B_4 synthesis by polymorphonuclear leukocytes from male patients with diabetes mellitus. Prostaglandins Leukot. Med. 14, 305 – 311.

96 Peters-Golden, M., Canetti, C., Mancuso, P. and Coffey, M. J. (2005) Leukotrienes: Underappreciated mediators of innate immune responses. J. Immunol. 174, 589 – 594.

97 Bailie, M. B., Standiford, T. J., Laichalk, L. L., Coffey, M. J., Strieter, R. and Peters-Golden, M. (1996) Leukotriene-deficient mice manifest enhanced lethality from *Klebsiella* pneumonia in association with decreased alveolar macrophage phagocytic and bactericidal activities. J. Immunol. 157, 5221 – 5224.

98 Malaviya, R. and Abraham, S. N. (2000) Role of mast cell leukotrienes in neutrophil recruitment and bacterial clearance in infectious peritonitis. J. Leukoc. Biol. 67, 841 – 846.

99 Benjamim, C. F., Canetti, C., Cunha, F. Q., Kunkel, S. L. and Peters-Golden, M. (2005) Opposing and hierarchical roles of leukotrienes in local innate immune versus vascular responses in a model of sepsis. J. Immunol. 174, 1616 – 1620.

100 Bafica, A., Scanga, C. A., Serhan, C., Machado, F., White, S., Sher, A. and Aliberti, J. (2005) Host control of *Mycobacterium tuberculosis* is regulated by 5-lipoxygenase-dependent lipoxin production. J. Clin. Invest. 115, 1601 – 1606.

101 Peres, C., de Paula, L., Medeiros, A., Sorgi, C., Soares, E., Carlos, D., Peters-Golden, M., Silva, C. and Faccioli, L. (2007) Inhibition of leukotriene biosynthesis abrogates the host control of *Mycobacterium tuberculosis*. Microbes Infect. 9, 483 – 489.

102 Medeiros, A. I., Sa-Nunes, A., Soares, E. G., Peres, C. M., Silva, C. L. and Faccioli, L. H. (2004) Blockade of endogenous leukotrienes exacerbates pulmonary *Histoplasmosis*. Infect. Immun. 72, 1637 – 1644.

103 Gosselin J, Borgeat, P., Flamand L (2005) Leukotriene B_4 protects latently infected mice against murine cytomegalovirus reactivation following allogeneic transplantation. J. Immunol. 174, 1587 – 1593.

104 Chen, N., Restivo, A. and Reiss, C. S. (2001) Leukotrienes play protective roles early during experimental VSV encephalitis. J. Neuroimmunol. 120, 94 – 102.
105 Serezani, C. H., Perrela, J. H., Russo, M., Peters-Golden, M. and Jancar, S. (2006) Leukotrienes are essential for the control of *Leishmania amazonensis* infection and contribute to strain variation in susceptibility. J. Immunol. 177, 3201 – 3208.
106 Claesson, H., Lindgren, J. and Gustafsson, B. (1985) Opsonized bacteria stimulate leukotriene synthesis in human leukocytes. Biochim. Biophys. Acta 836, 361 – 367.
107 Mancuso, P., Standiford, T., Marshall, T. and Peters-Golden, M. (1998) 5-Lipoxygenase reaction products modulate alveolar macrophage phagocytosis of *Klebsiella pneumoniae.* Infect. Immun. 66, 5140 – 5146.
108 McCurdy, J. D., Olynych, T. J., Maher, L. H. and Marshall, J. S. (2003) Cutting edge: Distinct toll-like receptor 2 activators selectively induce different classes of mediator production from human mast cells. J. Immunol. 170, 1625 – 1629.
109 Surette, M. E., Palmantier, R., Gosselin, J. and Borgeat, P. (1993) Lipopolysaccharides prime whole human blood and isolated neutrophils for the increased synthesis of 5-lipoxygenase products by enhancing arachidonic acid availability: involvement of the CD14 antigen. J. Exp. Med. 178, 1347 – 1355.
110 Hattermann, K., Picard, S., Borgeat, M., Leclerc, P., Pouliot, M. and Borgeat, P. (2007) The Toll-like receptor 7/8-ligand resiquimod (R-848) primes human neutrophils for leukotriene B_4, prostaglandin E_2 and platelet-activating factor biosynthesis. FASEB J. 21, 1575 – 1585.
111 Olsson, S. and Sundler, R. (2007) The macrophage beta-glucan receptor mediates arachidonate release induced by zymosan: essential role for Src family kinases. Mol. Immunol. 44, 1509 – 1515.
112 Mancuso, P., Gottschalk, A., Phare, S. M., Peters-Golden, M., Lukacs, N. W. and Huffnagle, G. B. (2002) Leptin-deficient mice exhibit impaired host defense in gram-negative pneumonia. J. Immunol. 168, 4018 – 4024.
113 Coffey, M. J., Phare, S. M. and Peters-Golden, M. (2004) Role of leukotrienes in killing of *Mycobacterium bovis* by neutrophils. Prostaglandins Leukot. Essent. Fatty Acids 71, 185 – 190.
114 Castro, M., Morgenthaler, T. I., Hoffman, O. A., Standing, J. E., Rohrbach, M. S. and Limper, A. H. (1993) *Pneumocystis carinii* induces the release of arachidonic acid and its metabolites from alveolar macrophages. Am. J. Respir. Cell Mol. Biol. 9, 73 – 81.
115 Wolf, J. E., Massof, S. E. and Peters, S. P. (1992) Alterations in murine macrophage arachidonic acid metabolism following ingestion of nonviable *Histoplasma capsulatum.* Infect. Immun. 60, 2559 – 2564.
116 Gosselin, J. and Borgeat, P. (1997) Epstein-Barr virus modulates 5-lipoxygenase product synthesis in human peripheral blood mononuclear cells. Blood 89, 2122 – 2130.
117 Matsukawa, A., Hogaboam, C. M., Lukacs, N. W., Lincoln, P. M., Strieter, R. M. and Kunkel, S. L. (1999) Endogenous monocyte chemoattractant protein-1 (MCP-1) protects mice in a model of acute septic peritonitis: Cross-talk between MCP-1 and Leukotriene B_4. J. Immunol. 163, 6148 – 6154.
118 Zimmerman, B. J., Holt, J. W., Paulson, J. C., Anderson, D. C., Miyasaka, M., Tamatani, T., Todd, R. F., Rusche, J. R. and Granger, D. N. (1994) Molecular determinants of lipid mediator-induced leukocyte adherence and emigration in rat mesenteric venules. Am. J. Physiol. 266, H847-H853.
119 Tager, A. M., Bromley, S. K., Medoff, B. D., Islam, S. A., Bercury, S. D., Friedrich, E. B., Carafone, A. D., Gerszten, R. E. and Luster, A. D. (2003) Leukotriene B_4 receptor BLT1 mediates early effector T cell recruitment. Nat. Immunol. 4, 982 – 990.
120 Islam, S. A., Thomas, S. Y., Hess, C., Medoff, B. D., Means, T. K., Brander, C., Lilly, C. M., Tager, A. M. and Luster, A. D. (2006) The leukotriene B_4 lipid chemoattractant receptor BLT1 defines antigen-primed T cells in humans. Blood 107, 444 – 453.
121 Ott, V. L., Cambier, J. C., Kappler, J., Marrack, P. and Swanson, B. J. (2003) Mast cell-dependent migration of effector $CD8^+$ T cells through production of leukotriene B_4. Nat. Immunol. 4, 974 – 981.
122 Prinz, I., Gregoire, C., Mollenkopf, H., Aguado, E., Wang, Y., Malissen, M., Kaufmann, S. H. and Malissen, B. (2005) The type 1 cysteinyl leukotriene receptor triggers calcium influx and chemotaxis in mouse αβ- and γδ-effector T cells. J. Immunol. 175, 713 – 719.
123 Doepping, S., Funk, C. D., Habenicht, A. J. and Spanbroek, R. (2007) Selective 5-lipoxygenase expression in Langerhans cells and impaired dendritic cell migration in 5-LO-deficient mice reveal leukotriene action in skin. J. Invest. Dermatol. 127, 1692 – 1700.
124 Hebert, M. J., Takano, T., Holthofer, H. and Brady, H. R. (1996) Sequential morphologic events during apoptosis of human neutrophils. Modulation by lipoxygenase-derived eicosanoids. J. Immunol. 157, 3105 – 3115.
125 Lee, E., Robertson, T., Smith, J. and Kilfeather, S. (2000) Leukotriene receptor antagonists and synthesis inhibitors reverse survival in eosinophils of asthmatic individuals. Am. J. Respir. Crit. Care Med. 161, 1881 – 1886.
126 Wirth, J. J. and Kierszenbaum, F. (1985) Stimulatory effects of leukotriene B_4 on macrophage association with and intracellular destruction of *Trypanosoma cruzi.* J. Immunol. 134, 1989 – 1993.
127 Wirth, J. J. and Kierszenbaum, F. (1985) Effects of leukotriene C_4 on macrophage association with and intracellular fate of *Trypanosoma cruzi.* Mol. Biochem. Parasitol. 15, 1 – 10.
128 Demitsu, T., Katayama, H., Saito-Taki, T., Yaoita, H. and Nakano, M. (1989) Phagocytosis and bactericidal action of mouse peritoneal macrophages treated with leukotriene B_4. Int. J. Immunopharmacol. 11, 801 – 808.
129 Mancuso, P. and Peters-Golden, M. (2000) Modulation of alveolar macrophage phagocytosis by leukotrienes is Fc receptor-mediated and protein kinase C-dependent. Am. J. Respir. Cell. Mol. Biol. 23, 727 – 732.
130 Mancuso, P., Nana-Sinkam, P. and Peters-Golden, M. (2001) Leukotriene B_4 augments neutrophil phagocytosis of *Klebsiella pneumoniae.* Infect. Immun. 69, 2011 – 2016.
131 Canetti, C., Hu, B., Curtis, J. L. and Peters-Golden, M. (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 – 1883.
132 Marder, P., Sawyer, J., Froelich, L., Mann, L. and Spaethe, S. (1995) Blockade of human neutrophil activation by 2-[2-propyl-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxphenoxy] propoxy]phenoxy] benzoic acid (LY29311), a novel leukotriene B_4 receptor antagonist. Biochem. Pharmacol. 49, 1683 – 1690.
133 Serezani, C. H. C., Aronoff, D. M., Jancar, S., Mancuso, P. and Peters-Golden, M. (2005) Leukotrienes enhance the bactericidal activity of alveolar macrophages against *Klebsiella pneumoniae* through the activation of NADPH oxidase. Blood 106, 1067 – 1075.
134 Talvani, A., Machado, F. S., Santana, G. C., Klein, A., Barcelos, L., Silva, J. S. and Teixeira, M. M. (2002) Leukotriene B_4 induces nitric oxide synthesis in *Trypanosoma cruzi*-infected murine macrophages and mediates resistance to infection. Infect. Immun. 70, 4247 – 4253.
135 Yong, E. C., Chi, E. Y. and Henderson, W. R. J. (1994) *Toxoplasma gondii* alters eicosanoid release by human mononuclear phagocytes: role of leukotrienes in interferon gamma-induced antitoxoplasma activity. J. Exp. Med. 180, 1637 – 1648.
136 Coffey, M. J., Phare, S. M., George, S., Peters-Golden, M. and Kazanjian, P. H. (1998) Granulocyte colony-stimulating factor administration to HIV-infected subjects augments reduced leukotriene synthesis and anticryptococcal activity in neutrophils. J. Clin. Invest. 102, 663 – 670.

137 Moqbel, R., Sass-Kuhn, S., Goetzl, E. and Kay, A. (1983) Enhancement of neutrophil- and eosinophil-mediated complement-dependent killing of schistosomula of *Schistosoma mansoni in vitro* by leukotriene B_4. Clin. Exp. Immunol. 52, 519 – 527.

138 Serhan, C., Radin, A., Smolen, J., Korchak, H., B, S. and Weissmann, G. (1982) Leukotriene B_4 is a complete secretagogue in human neutrophils: A kinetic analysis. Biochem. Biophys. Res. Commun. 107, 1006 – 1012.

139 Flamand, L., Borgeat, P., Lalonde, R. and Gosselin, J. (2004) Release of anti-HIV mediators after administration of leukotriene B_4 to humans. J. Infect. Dis. 189, 2001 – 2009.

140 Dewald, B. and Baggiolini, M. (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 – 304.

141 Larfars, G. L. F., Devynck, M. A., Palmblad, J. and Gyllenhammer, H. (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 – 1405.

142 Bandeira-Melo, C., Hall, J. C., Penrose, J. F. and Weller, P. F. (2002) Cysteinyl leukotrienes induce IL-4 release from cord blood-derived human eosinophils. J. Allergy Clin. Immunol. 109, 975 – 979.

143 Bandeira-Melo, C., Woods, L. J., Phoofolo, M. and Weller, P. F. (2002) Intracrine cysteinyl leukotriene receptor-mediated signaling of eosinophil vesicular transport-mediated interleukin-4 secretion. J. Exp. Med. 196, 841 – 850.

144 Wan, M., Sabirsh, A., Wetterholm, A., Agerberth, B. and Haeggstrom, J. Z. (2007) Leukotriene B_4 triggers release of the cathelicidin LL-37 from human neutrophils: novel lipid-peptide interactions in innate immune responses. FASEB J. [Epub ahead of print].

145 Brach, M. A., de Vos, S., Arnold, C., Gruss, H. J., Mertelsmann, R. and Herrmann, F. (1992) Leukotriene B_4 transcriptionally activates interleukin-6 expression involving NK-chi B and NF-IL6. Eur. J. Immunol. 22, 2705 – 2711.

146 Poubelle, P., Stankova, J., Grassi, J. and Rola-Pleszczynski, M. (1991) Leukotriene B_4 up-regulates IL-6 rather than IL-1 synthesis in human monocytes. Agents Actions 34, 42 – 45.

147 Thompson, C., Cloutier, A., Bosse, Y., Thivierge, M., CL, G., Larivee, P., McDonald, P., Stankova, J. and Rola-Pleszczynski, M. (2006) CysLT1 receptor engagement induces activator protein-1- and NF-κB-dependent IL-8 expression. Am. J. Respir. Cell Mol. Biol. 35, 697 – 704.

148 Lötzer, K., Jahn, S., Kramer, C., Hildner, M., Nüsing, R., Funk, C. D. and Habenicht, A. J. R. (2007) 5-Lipoxygenase/cyclooxygenase-2 cross-talk through cysteinyl leukotriene receptor 2 in endothelial cells. Prostaglandins Other Lipid Mediat. doi:10.1016/j.prostaglandins.2007.04.005.

149 Del Prete, A., Shao, W. H., Mitola, S., Santoro, G., Sozzani, S. and Haribabu, B. (2007) Regulation of dendritic cell migration and adaptive immune response by leukotriene B_4 receptors: a role for LTB_4 in up-regulation of CCR7 expression and function. Blood 109, 626 – 631.

150 Thivierge, M., Stankova, J. and Rola-Pleszczynski, M. (2006) Toll-like receptor agonists differentially regulate cysteinyl-leukotriene receptor 1 expression and function in human dendritic cells. J. Allergy Clin. Immunol. 117, 1155 – 1162.

151 Ichiyama, T., Kajimoto, M., Hasegawa, M., Hashimoto, K., Matsubara, T. and Furukawa, S. (2007) Cysteinyl leukotrienes enhance tumour necrosis factor-alpha-induced matrix metalloproteinase-9 in human monocytes/macrophages. Clin. Exp. Allergy 37, 608 – 614.

152 Stankova, J. and Rola-Pleszczynski, M. (1992) Leukotriene B_4 stimulates *c-fos* and *c-jun* gene transcription and AP-1 binding activity in human monocytes. Biochem. J. 282, 625 – 629.

153 Qiu, H., Johansson, A. S., Sjostrom, M., Wan, M., Schroder, O., Palmblad, J. and Haeggstrom, J. Z. (2006) Differential induction of BLT receptor expression on human endothelial cells by lipopolysaccharide, cytokines, and leukotriene B_4. Proc. Natl. Acad. Sci. USA 103, 6913 – 6918.

154 Vaddi, K. and Newton, R. C. (1994) Regulation of monocyte integrin expression by beta-family chemokines. J. Immunol. 153, 4721 – 4732.

155 Runarsson, G., Liu, A., Mahshid, Y., Feltenmark, S., Pettersson, A., Klein, E., Bjorkholm, M. and Claesson, H. E. (2005) Leukotriene B_4 plays a pivotal role in CD40-dependent activation of chronic B lymphocytic leukemia cells. Blood 105, 1274 – 1279.

156 Dugas, N., Dugas, B., Kolb, J., Yamaoka, K., Delfraiss, J. F. and Damais, C. (1996) Role of leukotriene B_4 in the interleukin-4-induced human mononuclear phagocyte activation. Immunology 88, 384 – 388.

157 Yamaoka, K. A., Dugas, B., Paul-Eugene, N., Mencia-Huerta, J. M., Braquet, P. and Kolb, J. P. (1994) Leukotriene B_4 enhances IL-4-induced IgE production from normal human lymphocytes. Cell. Immunol. 156, 124 – 134.

158 Arcoleo, F., Milano, S., D'Agostino, P. and Cillari, E. (1995) Effect of exogenous leukotriene B_4 (LTB_4) on BALB/c mice splenocyte production of Th1 and Th2 lymphokines. Int. J. Immunopharmacol. 17, 457 – 463.

159 Dokter, W. H., Sierdsema, S. J., Esselink, M. T., Halie, M. R. and Vellenga, E. (1994) Interleukin-4-mediated inhibition of C-Fos mRNA expression: role of the lipoxygenase directed pathway. Leukemia 8, 1181 – 1184.

160 Milano, S., Arcoleo, F., Dieli, M., D'Agostino, R., De Nucci, G., D'Agostino, P. and Cillari, E. (1996) *Ex vivo* evidence for PGE_2 and LTB_4 involvement in cutaneous leishmaniasis: relation with infection status and cytokine production. Parasitology 112, 13 – 19.

161 Marcinkiewicz, J., Grabowska, A., Bryniarski, K. and Chain, B. (1997) Enhancement of $CD4^+$ T-cell-dependent interleukin-2 production *in vitro* by murine alveolar macrophages: the role of leukotriene B_4. Immunology 91, 369 – 374.

162 Stankova, J., Gagnon, N. and Rola-Pleszczynski, M. (1992) Leukotriene B_4 augments interleukin-2 receptor-beta (IL-2R beta) expression and IL-2R beta-mediated cytotoxic response in human peripheral blood lymphocytes. Immunology 76, 258 – 263.

163 Stankova, J., Dupuis, G., Gagnon, N., Thivierge, M., Turcotte, S. and Rola-Pleszczynski, M. (1993) Priming of human monocytes with leukotriene B_4 enhances their sensitivity in IL-2-driven tumor necrosis factor-α production: Transcriptional and post-transcriptional up-regulation of IL-2 receptors. J. Immunol. 150, 4041 – 4051.

164 Yamaoka, K. A. and Kolb, J. P. (1993) Leukotriene B_4 induces interleukin 5 generation from human T lymphocytes. Eur. J. Immunol. 23, 2392 – 2398.

165 Kuhns, D. B., Nelson, E. L., Alvord, W. G. and Gallin, J. I. (2001) Fibrinogen induces IL-8 synthesis in human neutrophils stimulated with formyl-methionyl-leucyl-phenylalanine or Leukotriene B_4. J. Immunol. 167, 2869 – 2878.

166 Aoki, Y., Qiu, D., Zhao, G. H. and Kao, P. N. (1998) Leukotriene B_4 mediates histamine induction of NF-κB and IL-8 in human bronchial epithelial cells. Am. J. Physiol. 274, L1030-L1039.

167 Huang, L., Zhao, A., Wong, F., Ayala, J. M., Struthers, M., Ujjainwalla, F., Wright, S. D., Springer, M. S., Evans, J. and Cui, J. (2004) Leukotriene B_4 strongly increases monocyte chemoattractant protein-1 in human monocytes. Arterioscler. Thromb. Vasc. Biol. 24, 1783 – 1788.

168 Wang, M. L., Huang, X. J., Fang, S. H., Yuan, Y. M., Zhang, W. P., Lu, Y. B., Ding, Q. and Wei, E. Q. (2006) Leukotriene D_4 induces brain edema and enhances CysLT2 receptor-mediated aquaporin 4 expression. Biochem. Biophys. Res. Commun. 350, 399 – 404.

169 Parhamifar, L., Jeppsson, B. and Sjolander, A. (2005) Activation of $cPLA_2$ is required for leukotriene D_4-induced proliferation in colon cancer cells. Carcinogenesis 26, 1988 – 1998.

170 Lee, K. S., Kim, S. R., Park, H. S., Park, S. J., Min, K. H., Lee, K. Y., Jin, S. M. and Lee, Y. C. (2007) Cysteinyl leukotriene upregulates IL-11 expression in allergic airway disease of mice. J. Allergy Clin. Immunol. 119, 141 – 149.
171 Lamoureux, J., Stankova, J. and Rola-Pleszczynski, M. (2006) Leukotriene D_4 enhances immunoglobulin production in CD40-activated human B lymphocytes. J. Allergy Clin. Immunol. 117, 924 – 930.
172 Mellor, E. A., Austen, K. F. and Boyce, J. A. (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 – 592.
173 Mellor, E. A., Frank, N., Soler, D., Hodge, M. R., Lora, J. M., Austen, K. F. and Boyce, J. A. (2003) Expression of the type 2 receptor for cysteinyl leukotrienes CysLT2R by human mast cells: Functional distinction from CysLT1R. Proc. Natl. Acad. Sci. USA 100, 11589 – 11593.
174 Machida, I., Matsuse, H., Kondo, Y., Kawano, T., Saeki, S., Tomari, S., Obase, Y., Fukushima, C. and Kohno, S. (2004) Cysteinyl leukotrienes regulate dendritic cell functions in a murine model of asthma. J. Immunol. 172, 1833 – 1838.
175 Menard, G. and Bissonnette, E. Y. (2000) Priming of alveolar macrophages by leukotriene D_4 : potentiation of inflammation. Am. J. Respir. Cell Mol. Biol. 23, 572 – 577.
176 Wong, G. W., Foster, P. S., Yasuda, S., Qi, J. C., Mahalingam, S., Mellor, E. A., Katsoulotos, G., Li, L., Boyce, J. A., Krilis, S. A. and Stevens, R. L. (2002) Biochemical and functional characterization of human transmembrane tryptase TMT / tryptase gamma TMT is an exocytosed mast cell protease that induces airway hyperresponsiveness *in vivo* via an interleukin-13/interleukin-4 receptor α/signal transducer and activator of transcription STAT 6-dependent pathway. J. Biol. Chem. 277, 41906 – 41915.
177 Shraga-Levine, Z., Ben-Menahem, D. and Naor, Z. (1996) Arachidonic acid and lipoxygenase products stimulate protein kinase Cβ mRNA levels in pituitary alpha T3 – 1 cell line: role in gonadotropin-releasing hormone action. Biochem. J. 316, 667 – 670.
178 Kawano, T., Matsuse, H., Kondo, Y., Machida, I., Saeki, S., Tomari, S., Mitsuta, K., Obase, Y., Fukushima, C., Shimoda, T. and Kohno, S. (2003) Cysteinyl leukotrienes induce nuclear factor kappa b activation and RANTES production in a murine model of asthma. J. Allergy Clin. Immunol. 112, 369 – 374.
179 Perng, D. W., Wu, Y. C., Chang, K. T., Wu, M., Chiou, Y. C., Su, K. C., Perng, R. P. and Lee, Y. C. (2006) Leukotriene C_4 induces TGF-β1 production in airway epithelium via p38 kinase pathway. Am. J. Respir. Cell Mol. Biol. 34, 101 – 107.