

# 5-Lipoxygenase Pathway, Dendritic Cells, and Adaptive Immunity

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Received 30 October 2003; revised 10 February 2004; accepted 11 February 2004

5-lipoxygenase (5-LO) pathway is the major source of potent proinflammatory leukotrienes (LTs) issued from the metabolism of arachidonic acid (AA), and best known for their roles in the pathogenesis of asthma. These lipid mediators are mainly released from myeloid cells and may act as physiological autocrine and paracrine signalling molecules, and play a central role in regulating the interaction between innate and adaptive immunity. The biological actions of LTs including their immunoregulatory and proinflammatory effects are mediated through extracellular specific G-protein-coupled receptors. Despite their role in inflammatory cells, such as neutrophils and macrophages, LTs may have important effects on dendritic cells (DC)-mediated adaptive immunity. Several lines of evidence show that DC not only are important source of LTs, but also become targets of their actions by producing other lipid mediators and proinflammatory molecules. This review focuses on advances in 5-LO pathway biology, the production of LTs from DC and their role on various cells of immune system and in adaptive immunity.

## INTRODUCTION

Leukotrienes (LTs) are an important family of eicosanoid lipid mediators derived from the metabolism of arachidonic acid (AA) and associated with asthma and allergic reactions [1]. In contrast to prostaglandins (PGs), which are produced from AA by the action of cyclooxygenase (COX) enzymes, LTs are made predominately by inflammatory cells like polymorphonuclear leukocytes [2], activated macrophages [3], and mast cells [4]. Dendritic cells (DC) are the major players in both innate and adaptive immunity [5]. Despite their important role as the most professional antigen-presenting cells (APC) of the immune system, DC possess the enzymatic machinery to convert AA to proinflammatory LTs [6, 7, 8, 9]. Since, all human DC phenotypes examined until now constitutively express the 5-LO pathway, the role of DC 5-LO-derived lipid mediators in the regulation of the proximal steps of the immune responses was recently suggested [8]. Primary immune response involves phenomena as diverse as antigen uptake by DC, their subsequent migration through multiple tissue barriers, homing in lymphoid organs, and antigen presentation to T cells [8, 9]. LTs could play roles in each of these events. It is known that LTs exert their effects through extracellular G-protein-coupled receptors. Among human tissues studied by Northern blot analysis, LTB<sub>4</sub> receptor messenger RNA (mRNA) is strongly expressed in both thymus [10] and lymph nodes (Spanbroek R. unpublished data), while CysLT1 receptor mRNA is expressed in spleen [11]. In addition, 5-LO-deficient mice show altered ovalbumin-dependent cellular

and humoral immune responses [12, 13]. These observations provided substantial support for an indispensable role of 5-LO pathway in the regulation of adaptive immunity. Since LTs display a great variety of biological effects, it is not surprising that cellular LT biosynthesis must be tightly regulated. Based in the current knowledge of 5-LO pathway regulation, it becomes obvious that cellular LT biosynthesis is modulated by multiple mechanisms, including gene expression, cytokine effects, enzyme movement, and compartmentalization of the 5-LO pathway. Thus the understanding of the precise regulatory mechanism of the 5-LO activity might provide new concepts for the development of anti-inflammatory drugs.

## 5-LO PATHWAY AND LT BIOSYNTHESIS

LTs are lipid messengers that play central role in immune responses and tissue homeostasis [14]. Biosynthesis of LTs from AA was initially described in polymorphonuclear leukocytes and monocytes. First described in 1937 as the slow reacting substances of anaphylaxis (SRS-A), these lipid mediators are now known as the cysteinyl LTs (CysLTs), LTC<sub>4</sub>, LTD<sub>4</sub> and LTE<sub>4</sub> [15]. Synthesis of LTs can be divided in two pathways: one to create CysLTs and another to create LTB<sub>4</sub> (Figure 1). Some of important properties of 5-LO pathway proteins are summarized in Table 1. 5-LO is the key enzyme in LT biosynthesis and is located in the nucleus in some cell types and in the cytosol of others [16]. 5-LO is 72- to 80-kd monomeric soluble protein containing one nonheme iron believed necessary for catalysis [17].

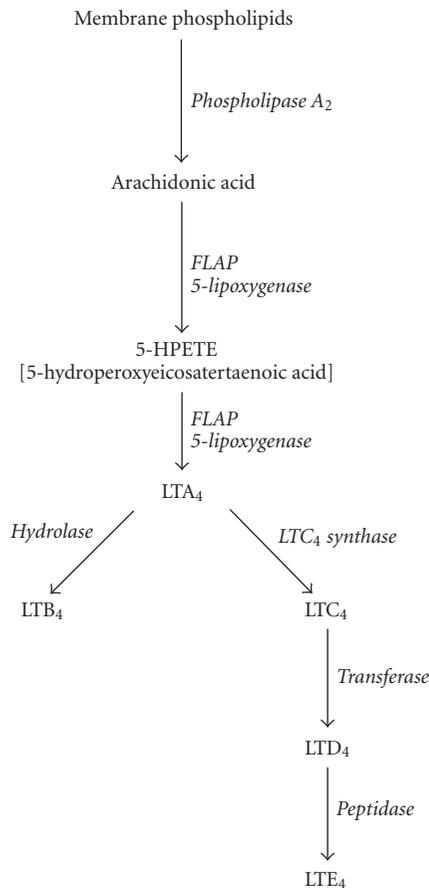


FIGURE 1. Pathways of LT biosynthesis. Arachidonic acid is liberated from membrane phospholipids by the action of cytosolic phospholipase A<sub>2</sub> (cPLA<sub>2</sub>) and presented to 5-LO enzyme by FLAP. 5-LO enzyme converts arachidonic acid to an unstable intermediate termed 5-hydroperoxyeicosatetraenoic acid (5-HPETE). Subsequently, 5-HPETE is dehydrated to yield the epoxide LTA<sub>4</sub>, a pivotal intermediate in the biosynthesis of inflammatory and anaphylactic mediators. Enzymatic hydrolysis of LTA<sub>4</sub> by LTA<sub>4</sub> hydrolase results in the formation of LTB<sub>4</sub>. Alternatively, LTC<sub>4</sub> synthase catalyzes the conjunction of LTA<sub>4</sub> with glutathione to form LTC<sub>4</sub>, which may be converted to LTD<sub>4</sub> and LTE<sub>4</sub> by the actions of the transferase and peptidase enzymes, respectively.

This enzyme possesses an NH<sub>2</sub>-terminal domain that binds to calcium iron and is essential for nuclear membrane translocation [18]. Active mainly in myeloid cells, such as monocytes, macrophages, B lymphocytes, granulocytes, mast cells, and DC, 5-LO requires Ca<sup>2+</sup> and is stimulated by ATP, phosphatidylcholine, lipids, and hydroperoxides [19]. Following cellular activation, 5-LO translocates to the nuclear membrane where it is able to interact with an 18-kd membrane-associated protein referred to as five-lipoxygenase-activating protein (FLAP). FLAP is an AA-binding protein whose function is to optimally present substrate to 5-LO [20]. The first evidence that the 18-kd protein is absolutely required for cellular

5-LO activity comes from transfection studies in human osteosarcoma cell lines [21]. In this system, expression of 5-LO alone resulted in no detectable cellular 5-LO activity following challenge with calcium ionophore A-23187. LT synthesis only occurred when 5-LO and FLAP were co-expressed in these cells. FLAP is expressed on T cells [22], macrophages, and DC [6], but not on erythrocytes or endothelial cells.

Cellular activation by immune complexes, bacterial peptides, and other stimuli elicit a sequence of events that include cytosolic phospholipase A<sub>2</sub> (cPLA<sub>2</sub>) and 5-LO translocation to the nuclear envelope to produce 5-hydroperoxy eicosatetraenoic acid (5-HPETE) from AA. Subsequently, 5-HPETE is dehydrated to yield the epoxide LTA<sub>4</sub>, a pivotal intermediate in the biosynthesis of inflammatory and anaphylactic mediators. LTA<sub>4</sub> undergoes transformation by one or more of three possible fates depending on the cellular context: hydrolysis, conjugation with glutathione, or transcellular metabolism to generate bioactive lipid mediators [23]. In neutrophils and monocytes, LTA<sub>4</sub> is converted predominately to the chemoattractant LTB<sub>4</sub> by LTA<sub>4</sub> hydrolase [24], but in human eosinophils, mast cells, and basophils, LTA<sub>4</sub> is conjugated with reduced glutathione by LTC<sub>4</sub> synthase to form the first of the CysLTs, LTC<sub>4</sub> [25]. After carrier-mediated cellular export, sequential cleavage of the glutathionyl side chain of LTC<sub>4</sub> generates the extracellular metabolites LTD<sub>4</sub> and LTE<sub>4</sub>. LTB<sub>4</sub> may be degraded by microsomal ω-oxidation and peroxisomal β-oxidation in myeloid cells and hepatocytes. Degradation is accompanied by loss of biological activity. It is important to note that degradative enzymes are increased by the transcription factor peroxisome proliferator-activated receptor α (PPARα) and this nuclear hormone receptor is in turn activated by binding with LTB<sub>4</sub> [26]. This feedback loop limits the duration of action of LTB<sub>4</sub>.

## RECEPTORS FOR LEUKOTRIENES

The actions of LTs require the expression of extracellular G-protein-coupled receptors (GPCR) which are members of the rhodopsin-like receptor superfamily. LTB<sub>4</sub> is a potent chemoattractant that is primarily involved in inflammation, immune responses, and host defense against infection. LTB<sub>4</sub> activates inflammatory cells by binding to its cell-surface receptor (designated BLT) via two known receptors, BLT1 and BLT2, according to the affinity of LTB<sub>4</sub> for the receptor. BLT1 has been characterized as a 43-kd GPCR expressed only in inflammatory cells, including neutrophils, alveolar macrophages, and eosinophils and with a high affinity for only LTB<sub>4</sub> [27]. The second G-protein-coupled receptor for LTB<sub>4</sub>, BLT2 receptor, has only recently been described and is a low-affinity receptor expressed more ubiquitously [28, 29]. Both receptors are found in lymph node [30] on the same chromosome, but intriguingly, the promoter region of the BLT1 gene is localized within the open reading frame (ORF) of the BLT2 gene, which encodes a low-affinity

TABLE 1. 5-lipoxygenase pathway proteins.

5-lipoxygenase	FLAP	LTA <sub>4</sub> hydrolase	LTC <sub>4</sub> synthase
78 kd, cytosolic protein	18 kd, membrane protein	69 kd, cytosolic protein	18 kd, membrane protein
673 amino acid	AA-binding protein	Converts LTA <sub>4</sub> to LTB <sub>4</sub>	Converts LTA <sub>4</sub> to LTC <sub>4</sub>
Nonheme iron	Required for activation of 5-LO		
Translocated to cell membrane after cell activation			
Dioxygenase activity converts AA to 5-HPETE			
Dehydratase activity converts 5-HPETE to LTA <sub>4</sub>			

receptor for LTB<sub>4</sub> [27]. The high-affinity receptor BLT1 mediates chemotaxis, chemokinesis, aggregation, and adherence to endothelium. The low-affinity receptor BLT2 mediates degranulation and oxygen radical release [31]. Overexpression of LTB<sub>4</sub> receptors in leukocytes leads to increased neutrophil influx into the lungs after ischemia-reperfusion in mice [32]. It is also important to indicate that LTB<sub>4</sub> can bind and activate the intranuclear transcription factor PPAR $\alpha$ , resulting in the activation of genes that terminate inflammatory processes [10]. The receptor for cysteinyl LTs, LTC<sub>4</sub>, LTD<sub>4</sub>, and LTE<sub>4</sub> are named CysLT receptors and are distinct from the LTB<sub>4</sub> receptors. Two classes of CysLT receptors have been identified: CysLT1 and CysLT2 according to their sensitivity to selective LT receptor antagonists. CysLT1 has been identified in human smooth muscle cells [11], vascular endothelial cells [33], lung macrophages, and peripheral blood leukocytes. CysLT2 receptor, originally found in pulmonary vein preparations [34] by pharmacological assays, is detected in spleen, Purkinje fibers of the heart, and discrete region of the adrenal gland by molecular methods.

### REGULATORY MECHANISMS OF CELLULAR LT BIOSYNTHESIS

Abnormal production of LT contributes to a variety of inflammatory diseases, including asthma, glomerulonephritis, psoriasis, inflammatory bowel diseases, and acute lung injury [35]. Considering their important role in host defense against microbial infections [36], biosynthesis of LTs must be tightly regulated. Two steps seem to be involved in the control of LT biosynthesis, that is, liberation of AA and regulation of 5-LO activity [37]. Moreover, the expression of 5-LO and FLAP, which are subject to regulation in monocytic cells [38], have been considered as the major determinant of cellular LT biosynthesis [39]. 5-LO activity and product generation at sites of inflammation might be modulated in multiple ways. The most obvious would be the recruitment and stimulation of additional inflammatory cells. Another possibility is modulating the expression of enzymatic components

through transcriptional or posttranscriptional mechanisms. Recently, it has been reported that cyclic AMP (cAMP) elevating agents, such as PGE<sub>2</sub>, inhibited LT biosynthesis and 5-LO translocation to the nucleus in cytokine-primed human neutrophils [40]. The intracellular compartmentalization of the 5-LO metabolism affects the integrated output of this biosynthetic pathway [41]. Nuclear import of 5-LO can modulate LT production, since nuclear import can strongly enhance [42] or suppress [43] 5-LO activity. In considering the question of 5-LO translocation and its cellular localization, it is necessary to consider that 5-LO can move in or out of the nucleus in response to *in vivo* or *in vitro* experimental conditions [41]. Cytokines and other components may also affect 5-LO pathway, and the expression of 5-LO and FLAP can be controlled by specific molecules. For example, it has been reported that the Th2-derived cytokines, IL-4, and IL-13 inhibited the release of LT from monocytes by decreasing FLAP mRNA and protein levels, whereas, IL-1 and IFN $\gamma$  (Th1 cytokines) stimulate 5-LO expression [39]. 5-LO activity may be modulated by nitric oxide (NO) since prolonged exposure to lipopolysaccharide inhibits macrophage 5-LO metabolism via induction of NO synthesis [44]. In bone marrow-derived DC, we have recently demonstrated that exogenous or PGE<sub>2</sub>-induced IL-10 inhibited FLAP expression without any effect on 5-LO enzyme [6]. The regulatory mechanisms of the 5-LO pathway appear to be complex and depends on the composition of the investigated cell populations. Specific control of 5-LO pathway has long been suspected because expression of 5-LO activity is tissue specific and narrowly distributed to inflammatory cells. It is also important to note that there is wide variation in 5-LO activity and in 5-LO and FLAP levels even among different inflammatory cell types.

### 5-LO PATHWAY AND CELLS OF IMMUNE SYSTEM: WHAT ABOUT DENDRITIC CELLS?

One of the best known and most well-studied LTs is LTB<sub>4</sub>. LTB<sub>4</sub> is produced by many cells of the immune

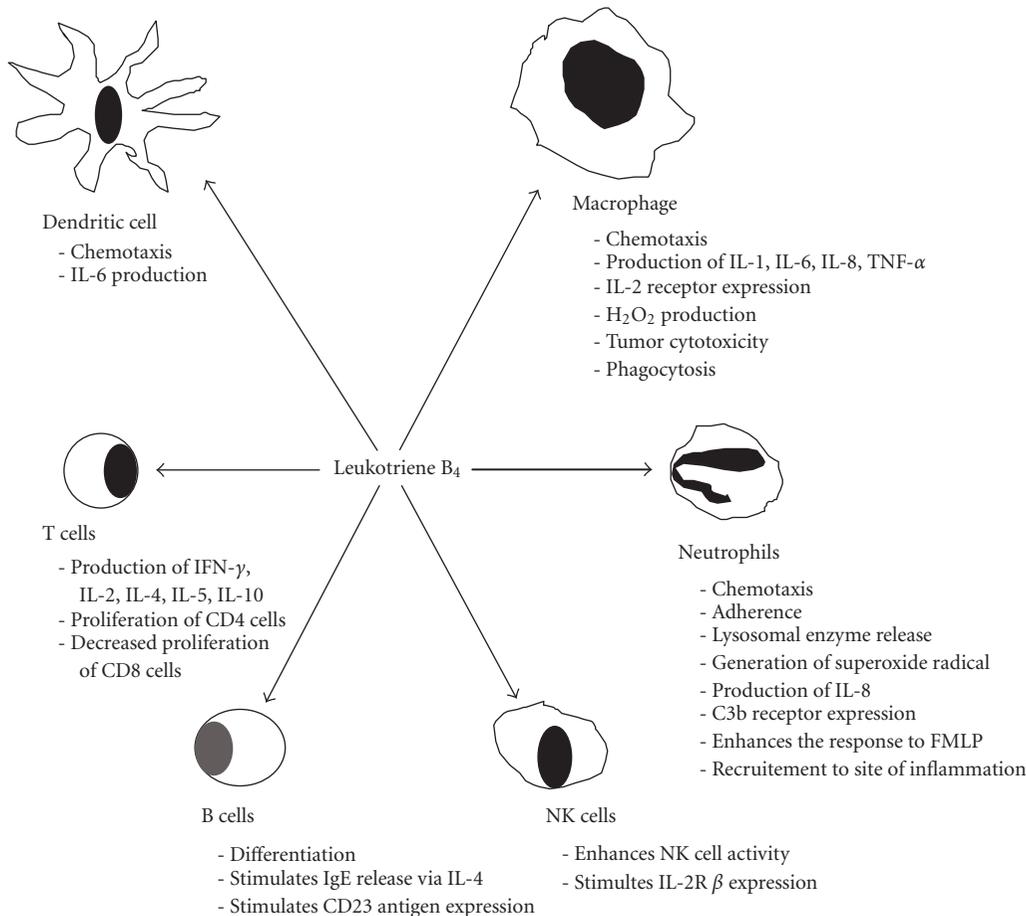


FIGURE 2. Effects of LTB<sub>4</sub> on cells of immune system.

system, including activated neutrophils stimulated with AA or calcium ionophore [45], macrophages, DC, and T cells [46, 47]. This lipid mediator has diverse effects on the function and activities of cells of the immune system (Figure 2). Several observations have suggested that LTB<sub>4</sub>, in cooperation with monocytes, stimulates T-suppressor-cell functions [48, 49]. These effects appeared to be exerted through inhibition of T CD4<sup>+</sup> (helper/inducer) subsets and enhancement of T CD8<sup>+</sup> (suppressor/cytotoxic) subsets [50]. The suppression required the presence of monocytes and was induced by the cyclooxygenase inhibitors [51]. It has been suggested that the mechanism of action involved induction of monocytes to produce both prostaglandins (metabolites of cyclooxygenase pathways) and cytokines, such as IFN- $\gamma$ , IL-2, which in turn lead to the production of IL-1 [52, 53]. Thus, the effects of LTB<sub>4</sub> on T lymphocytes are not the result of a direct action on lymphocytes themselves but an indirect action via monocytes. On natural killer (NK) cells, LTB<sub>4</sub> significantly augmented NK cell cytotoxicity and stimulated the expression of IL-2  $\beta$  receptors when added to effector target cocultures [54, 55]. LTB<sub>4</sub> is also known to enhance B cell

differentiation and secretion of IgE via an IL-4-dependent mechanism [56]. LTB<sub>4</sub> causes adhesion and chemotactic movement of leukocytes and stimulates aggregation, enzyme release, and generation of superoxide in neutrophils. Leukotrienes C<sub>4</sub>, D<sub>4</sub>, and E<sub>4</sub>, which are released from the lung tissue of asthmatic subjects exposed to specific allergens, seem to play a pathophysiological role in immediate hypersensitivity reactions. The expression of 5-LO and FLAP genes have been reported in human B cells by reversed transcription chain analysis [22]. Several AA-derived lipid mediators possess immunoregulatory properties *in vivo* and *in vitro*. The most interesting example is PGE<sub>2</sub>, which clearly affects the functions of DC and other cell types of the immune system [57]. In contrast to PGE<sub>2</sub>, LTB<sub>4</sub> is considered as a mainly immunopotentiating mediator, which stimulates the activity of NK cells and B lymphocytes, although it also induces suppressor function among human mononuclear leukocytes. LTB<sub>4</sub> can augment proliferation of mixed T lymphocytes and of OKT8<sup>+</sup> cells [58]. It also stimulates the release of IL-1 and TNF- $\alpha$  in human monocytes [59], and IL-8 from human polymorphonuclear leukocytes [60].

Cells that produce LTs or become targets to their actions can also produce other proinflammatory molecules, such as PGs, and various cytokines. For example, the exogenously added or the endogenously produced LTB<sub>4</sub> can enhance the release of IL-6 from human monocytes [61] and mice DC [6]. This may constitute an important mean by which monocytes and DC modulate inflammatory responses. Several lines of evidence support an expanded role of the 5-LO pathway in the regulation of antigen-specific adaptive immunity. Epidermal Langerhans cells (LC), a member of the DC family capable of initiating antigen-specific immune responses in naive lymphocytes, markedly express the 5-LO pathway [9]. We have recently demonstrated that mice bone marrow-derived DC (BM-DC) produce LTB<sub>4</sub> and other AA metabolites, which have an autocrine actions in APC-mediated immunity [6, 7]. Other investigators have reported the expression of 5-LO in human DC generated from CD34<sup>+</sup> hematopoietic progenitors and in lymphoid organs [8]. It has been recently reported that BM-DC express CysLT1 receptors, 5-LO, FLAP, and LTC<sub>4</sub> synthase, and produce CysLTs in response to aeroallergen [62]. The produced CysLTs play a crucial role in regulating DC function in a murine model for asthma. The ability of DC to migrate to lymphoid nodes may be affected by 5-LO products since the LTC<sub>4</sub> transporter MRP1 may regulate CCL19-dependent mobilization of DC from peripheral tissues to lymph nodes [63]. Taken together, these data suggest that by producing proinflammatory LTs and other components, DC and other APC may play important role in inflammatory processes and allergic diseases.

### CONCLUDING REMARKS

The main function of the immune system is the defence of the host against pathogens and tumors. Two major defence systems are involved in host defence against infectious agents and tumors: the innate and adaptive immunity, which differ in the means by which they recognize antigens. However, it is important to indicate that innate immune system activates, orientates, and regulates the adaptive immunity, which through clonal expansion of lymphocytes will respond to pathogen in antigen specific manner. Both innate and adaptive immunity are closely linked, and the interactions between the two systems of the host defence are regulated by a variety of cells and their mediators in particular cytokines and AA-derived lipid mediators, such as LTs.

The development of specific agonists and antagonists for each LT receptors will provide important reagent for further defining the biological and pathological actions of proinflammatory LTs. Other lipoxygenase products will also certainly receive attention in the year to come. To delineate molecular mechanisms within immune responses that are affected by 5-LO pathway products, future studies should be directed toward DC/T lymphocytes interactions, the identification of LT receptor-expressing cells

in lymphoid organs, and immune response studies of 5-LO knockout mice. Finally, further studies of LT receptors expression in different types of DC and other APC are needed to truly assess the potential roles of 5-LO pathway in DC biology and APC-mediated immunity.

### ACKNOWLEDGMENT

This work is supported by La Ligue Régionale Contre le Cancer, Comité Départemental des Charentes et de la Gironde.

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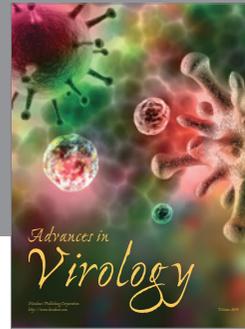
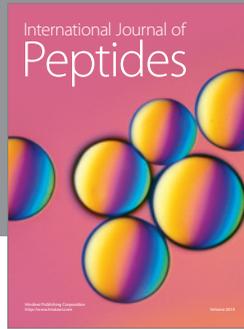
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