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Regulation of Immune Cells by Eicosanoid Receptors

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Eicosanoids are potent, bioactive, lipid mediators that regulate important components of the immune response, including defense against infection, ischemia, and injury, as well as instigating and perpetuating autoimmune and inflammatory conditions. Although these lipids have numerous effects on diverse cell types and organs, a greater understanding of their specific effects on key players of the immune system has been gained in recent years through the characterization of individual eicosanoid receptors, the identification and development of specific receptor agonists and inhibitors, and the generation of mice genetically deficient in various eicosanoid receptors. In this review, we will focus on the receptors for prostaglandin D_2, DP_1 and DP_2/CRTH2; the receptors for leukotriene B_4, BLT_1 and BLT_2; and the receptors for the cysteinyl leukotrienes, $CysLT_1$ and $CysLT_2$, by examining their specific effects on leukocyte subpopulations, and how they may act in concert towards the development of immune and inflammatory responses.

KEYWORDS: prostaglandin D_2, DP_1, DP_2, CRTH2, leukotriene B_4, BLT_1, BLT_2, cysteinyl leukotriene, $CysLT_1$, $CysLT_2$

INTRODUCTION

Eicosanoids comprise a family of 20-carbon–based lipid mediators derived from arachidonic acid, possessing multiple diverse functions on cells of the immune system. Upon liberation from the cell membrane by cytosolic phospholipase A_2 (PLA_2), arachidonic acid (AA) is rapidly metabolized into two major classes of eicosanoids, prostaglandins and leukotrienes, both of which are associated with numerous inflammatory, infectious, and ischemic processes. While the production and regulation of these lipid mediators are discussed in a separate paper in this issue[1], this review will outline their major effects on cellular subpopulations of the immune system through their specific receptor usage. In allergic and inflammatory conditions, levels of prostaglandin D_2, leukotriene B_4, and the cysteinyl leukotrienes LTC_4, LTD_4, and LTE_4 are linked to heightened leukocyte infiltration into affected tissues. Recent studies defining how these lipid mediators orchestrate complex pathways of leukocyte migration, degranulation, and mediator release through their specific receptor usage will be reviewed.

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THE PROSTAGLANDIN RECEPTORS DP_1 AND DP_2/CRTH2

Prostaglandin D_2 (PGD_2) is the predominant prostaglandin generated by activated mast cells and has been long associated with inflammation and allergic responses, as demonstrated by elevated levels of PGD_2 within bronchoalveolar lavage fluids[2] and in allergic skin biopsies[3] of antigen-challenged patients. DP_1, the first identified receptor for PGD_2, is a prostanoid G-protein coupled–type receptor with 73% homology at the amino acid level between the human and mouse forms[4]. DP_1 preferentially binds the ligand PGD_2 with a K_d of 1.5 n*M*, in addition to the selective DP_1 agonist BW245C and DP_1 antagonist BWA868C with equal affinities, and binds with 100-fold or less affinity to PGE_2, $PGF_{2\alpha}$, iloprost, and the thromboxane A_2 mimetic U46619. Binding of DP_1 by PGD_2 results in the elevation of intracellular cyclic AMP (cAMP) levels and Ca^{2+} mobilization, but not the production of inositol 1,4,5-triphosphate (IP_3)[5]. In organ tissues, DP_1 is expressed at low levels in the small intestine and retina in humans[5], while in mice, DP_1 is found in the ileum, lung, stomach, and uterus[6]. In the original description of human DP_1, basophils were the only human leukocytes found to express DP_1, but since then, DP_1 message has been demonstrated in human eosinophils[7], monocytes, dendritic cells[8], and Th1 and Th2 cells[9] at low levels. In mice, monocytes, dendritic cells[8], and eosinophils[10] express DP_1. In an ovalbumin (OVA)-induced murine model of asthma, mice deficient in the DP_1 receptor demonstrated decreased levels of eosinophils and lymphocytes, and the cytokines IL-4, IL-5, and IL-13, suggesting that DP_1 plays a critical role in the induction of Th2-mediated allergic responses[11] (Table 1).

TABLE 1
DP_1 and DP_2/CRTH2 Receptors

	DP_1	DP_2/CRTH2
Receptor expression on leukocytes	*Human*: eosinophils, basophils, monocytes, dendritic cells, Th1 and Th2 cells	*Human*: Th2 cells, type 2 cytotoxic cells, basophils, eosinophils, monocytes
	Mouse: monocytes, dendritic cells, eosinophils	*Mouse*: Th1 and Th2 cells, eosinophils, monocytes, mast cell
Agonists	$PGD_2 = PDJ_2$ BW245C ZK110841 SQ27986	$PGD_2 = PGJ_2 = 15d\text{-}PGD_2 =$ $DK\text{-}PGD_2 > \Delta^{12}\text{-}PGJ_2$ indomethacin
Antagonists	BWA868C AH6809	BM7 (neutralizing antibody) Ramatroban (BAY-u3405)

However, certain data suggested that PGD_2 might activate leukocytes through an alternate receptor to DP_1. In the OVA-induced asthma model, DP_1 up-regulation in the lung primarily occurs on the airway epithelium, and serum IgE levels and Th2 cytokine production by antigen-stimulated splenocytes from DP_1-deficient mice is preserved, indicating intact immune responses[11]. Activation of DP_1 through $G_{s\alpha}$ proteins results in an increase of intracellular cAMP typically associated with dampening of cellular effector function, contrary to the immune cell activation observed in PGD_2-high states, such as asthma and allergic responses. In addition, PGD_2 induces eosinophil chemotaxis, CD11b expression, and L-selectin expression in a manner neither replicated by the DP_1 receptor agonist BW245C nor inhibited by DP_1 receptor antagonist BWA868C[12], leading investigators to postulate that there existed a separate PGD_2 receptor whose proinflammatory functions were diametrically opposed to the suppressive effects of DP_1 activation.

In 1999, Nagata et al. described a novel, cell surface molecule expressed in Th2 cells,[13] eosinophils, and basophils, which they named CRTH2 (chemoattractant receptor-homologous molecule expressed on Th2 cells) that responded to a mast cell–derived factor. Subsequently, they identified PGD_2

as the mast cell–derived ligand for CRTH2, which is now also known as DP_2. Unlike DP_1 and the other prostanoid receptors, DP_2 phylogenetically shares more characteristics with the formyl peptide-like receptors (FPRs), a group of receptors that includes the chemoattractant C5a receptor and the leukotriene receptors BLT_1 and $CysLT_1$[14]. Activation of DP_2 leads to depression of intracellular cAMP levels, Ca^{2+} mobilization, and generation of diacylglycerol (DAG) and IP_3 through G_i protein signaling[15]. DP_2 mRNA is ubiquitously expressed in various human tissues, including the brain, heart, intestine, thymus, spleen, liver, and small and large intestine[16], while in the mouse, DP_2 mRNA is found at low levels in the lung, liver, kidney, brain, heart, thymus, and spleen[17]. In human peripheral blood leukocytes, DP_2 is found on Th2 cells, type 2 cytotoxic T (Tc2) cells, basophils, eosinophils, and in low quantities on monocytes, but not on Th1 cells, CD 19^+ B cells, NK cells, immature dendritic cells, or neutrophils[8,16]. In sharp contrast, mouse DP_2 is expressed on both Th1 and Th2 cellular subsets[17], in addition to eosinophils and monocyte, mast cell, and B cell lines[10] (Table 1).

DP_1 and DP_2 and T Cells

The DP_2 receptor was first identified as an orphan G-protein coupled chemoattractant receptor selectively expressed on human Th2 cells[13]. In one study characterizing human peripheral blood mononuclear cells (PBMCs), a small percent of $CD4^+$ T cells (0.4–6.5%) and $CD8^+$ T cells (3.5%) were DP_2 -positive, with the majority of the DP_2 -positive $CD4^+$ T cells being activated effector/memory T cells as indicated by $CD45RA^-$, $CD45RO^+$, and $CD25^+$ staining[13]. Subsequent studies confirmed that DP_2 identifies Th2 and Tc2 cells more specifically than either CCR3 or CCR4, two other chemoattractant receptors preferentially expressed on Th2 cells[18]. In keeping with known chemoattractant properties of its FPR structure, DP_2 activation by PGD_2 and the DP_2-specific agonist 13,14-dihydro-15-keto PGD_2 (DK-PGD_2) induces chemotaxis[14] and CD11b up-regulation[9] in Th2 cells, while the DP1 agonist BW245C does not. PGD_2 induces Th2 cell production of IL-4, IL-5, and IL-13, a result that is replicated to a lesser extent by the DK-PGD_2, but not BW245C, indicating activity through DP_2[9,19]. These results demonstrate that DP_2 amplifies Th2 cell responses by inducing their migration, enhancing their adhesiveness to endothelial surfaces by increasing CD11b surface expression, and invoking further elaboration of Th2 cytokines.

Although early studies did not demonstrate significant DP_1 expression in human T cells[14], addition of PGD_2 or the DP_1 agonist BW245C to CD3/CD28-stimulated CD4 and CD8 cells isolated from PBMCs results in decreased interferon (IFN)-γ and IL-2 production, while the DP_2 agonist DK-PGD_2 has no effect on the production of these cytokines, indicating this PGD_2 effect is mediated through selective DP_1 activation[9]. In addition, selective DP_1 stimulation decreases the number of IL-4-secreting Th2 cells in a dose-dependent manner, but has no discernible effect on IL-2, IL-5, or IL-13 production. On increasing the numbers of cycles in reverse transcription polymerase chain reaction (RT-PCR), DP_1 mRNA becomes detectable in both Th1 and Th2 cells at low levels[9]. However, competitive binding assays show that DP_2 is the dominant receptor on Th2 cells by preferentially binding PGD_2 over DP1[19]. Therefore, these studies demonstrate that DP_1 may provide a counter-regulatory effect on Th2 cells in opposition to DP_2, suggesting that DP_2 antagonists may actually further suppress Th2 responses not only by blocking DP_2, but also by increasing the availability of PGD_2 to bind DP_1 that would otherwise activate DP_2.

Although mouse DP_2 shares significant homology with the human DP_2 receptor, a significant distinction between the two species is the fact that DP_2 is expressed on both Th1 and Th2 subsets in mice[17], suggesting that a strict dichotomy between DP_2 regulation of Th1 and Th2 subsets may not exist in this species. Surprisingly, $DP_2^{-/-}$ mice on a C57Bl/6 background develop increased eosinophilia in an OVA-induced model of asthma, and *in vitro* CD3/CD28 stimulation of T cells from $DP_2^{-/-}$ mice generates significantly more IL-5 than wild-type T cells[20], suggesting that DP_2 may actually play an anti-inflammatory role in mice by suppressing T-cell production of Th2 cytokines in mice. $DP_2^{-/-}$ mice on both C57Bl/6 and Balb/c backgrounds generated by a separate group reportedly do not display significant differences in pulmonary infiltration in an asthma model nor in splenocyte production of IL-4, IL-5, or IFN-γ compared with wild-type mice[21]. While Balb/c $DP_2^{-/-}$ mice exhibit decreased swelling and

leukocyte infiltration in an IgE-mediated cutaneous reaction model, this clinical finding is not associated with significant changes in IL-4 or IFN-γ production[21]. These results contrast previous studies in which administration of the DP_2 selective agonist DK-PGD_2 exacerbates mouse models of asthma and atopic dermatitis[10], which instead suggest a proinflammatory role for murine DP_2.

These collective studies clearly indicate a dominant role for DP_2 in the direct activation of Th2 cells in humans. Although data suggest that DP_1 activation of T cells may play a counter-regulatory role by suppressing cytokine production and inhibiting leukocyte movement, the precise physiological relevance of DP_1 receptor activation on human Th1 and Th2 cells still remains to be defined more fully, requiring further dedicated studies of DP_1 activation on separate Th1 and Th2 cellular populations. In mice, the role of DP_2 activation on T cells and its role in disease pathogenesis is less well delineated, with the coincident existence of DP_2 on both Th1 and Th2 populations and conflicting phenotypes in allergic disease models, indicating that DP_2 may not play as critical a role in inducing Th2 responses in mice as in humans.

DP_1 and DP_2 in Eosinophils and Basophils

PGD_2 is a major eicosanoid product of mast cells, and levels of PGD_2 are elevated in allergic responses, suggesting an important role for PGD_2 in eosinophil activation. Addition of PGD_2 to eosinophils induces a number of proinflammatory responses, including chemokinesis, degranulation, and leukotriene production. Both PGD_2 receptors, DP_1 and DP_2, are expressed on human basophils[14] and eosinophils[7,22]. Through the use of DP_1- and DP_2-specific agonists, DP_2 has been identified as the critical receptor for eosinophil chemokinesis, chemotaxis, CD11b up-regulation, and degranulation, while selective DP_1 activation inhibits eosinophil apoptosis in culture conditions[7,12]. PGD_2 also induces similar responses in basophils through DP_2 activation, although DP_1 stimulation does not have antiapoptotic effects in this population[23]. Pretreatment of eosinophils with PGD_2 enhances their chemotaxis towards eotaxin-1 and 5-oxo-6,8,11,14-eicosatetraenoic acid (5-oxo-ETE) through activation of the DP_2 receptor, while PGD_2 activation of DP_2 suppresses basophil chemotaxis to these agents, indicating that DP_2 activation may preferentially augment eosinophil migration towards other subsequently encountered chemoattractants[24]. Therefore, although DP_1 and DP_2 are coexpressed on eosinophils and bind to PGD_2 with roughly equal affinities[14], DP_2 appears to exert a dominant proinflammatory effect on these cells. This effect may be explained, in part, by the relatively low expression of DP_1 on eosinophils compared with DP_2, which may up-regulated under inflammatory conditions[15].

PGD_2 is short lived *in vivo*, but its metabolic and degradation products also retain specific biologic activities that have been studied in eosinophils, shedding further light on selective DP_1 and DP_2 activation. PGJ_2 is the initial dehydration product of PGD_2, which can then be further metabolized to 15-dexoxy-$\Delta^{12,14}$-PGJ_2 (15d-PGJ_2) and Δ^{12}-PGJ_2, all of which are found in blood plasma incubated with PGD_2[25]. While PGJ_2 binds to both DP_1 and DP_2, 15d-PGD_2 selectively binds DP_2 over DP_1[14]. At low concentrations (10^6–10^9 *M*), 15d-PGJ_2 induces eosinophil calcium flux, actin polymerization, and CD11b expression, while it has no effect on DP_1-mediated platelet aggregation[26]. These results contrast previous findings that 15d-PGJ_2 (at micromolar concentrations) possesses anti-inflammatory effects by inhibiting monocyte cytokine production and release through activation of peroxisome proliferator-activated receptor-γ (PPARγ)[27]. Δ^{12}-PGJ_2 also induces chemotaxis and respiratory burst in eosinophils, as well as enhances eosinophil movement to CCL11/eotaxin-1 and mobilization from the bone marrow[28]. Although Δ^{12}-PGJ_2 binds with weak affinity to both DP_1 and DP_2[14], DP_1 activation does not lead to significant calcium flux or chemotaxis in eosinophils, leading the authors to hypothesize that these proinflammatory Δ^{12}-PGJ_2–mediated effects on eosinophils occur through DP_2 stimulation rather than DP_1.

In mice as in humans, both DP_1 and DP_2 are expressed on eosinophils. In *in vitro* chemotaxis studies, PGD_2 induces migration of eosinophils by activation of DP_2, while DP_1 activation has no such effect.

Addition of the DP_2 agonist DK-PGD_2 increases organ eosinophilia in models of OVA-induced asthma and atopic dermatitis in mice[10], suggesting that DP_2 contributes to eosinophil infiltration in allergic disease by inducing their movement into inflamed tissues. However, replication of the asthma model in mice lacking the two PGD_2 receptors has paradoxically yielded opposite results. $DP_1^{-/-}$ mice have decreased airway eosinophilia in an OVA-induced asthma model[11], while $DP_2^{-/-}$ mice display either no difference in lung leukocyte infiltration or increased airway eosinophilia in separate studies[20,21]. An IgE-mediated inflammatory cutaneous reaction is suppressed in $DP_2^{-/-}$ mice, however, with significantly decreased ear swelling and dermal leukocyte infiltration, including lymphocytes, eosinophils, neutrophils, and mast cells[21].

These data suggest that the role of PGD_2 in inducing eosinophilic inflammation in mice occurs by mechanisms more complex than directly inducing eosinophil activation and movement. Although *in vitro* studies show that DP_2 is capable of directly activating eosinophils, *in vivo* PGD_2-mediated allergic effects may depend on cooperation of resident cells that are organ -or site-specific. In murine lungs, DP_1 is primarily expressed on the epithelial cells of the bronchioles and type II alveolar epithelial cells, with lower expression in the type I alveolar epithelial cells and leukocytes[11]. It is hypothesized that DP_1-activated airway epithelium is required for production of cytokines and chemokines, leading to Th2 cell and eosinophil recruitment into the lung. Therefore, in murine pulmonary allergic reactions, PGD_2 may play a predominant role by activating DP_1 receptors on epithelium and generating eosinophil chemoattractants other than PGD_2, which would be consistent with the findings that $DP_2^{-/-}$ mice do not exhibit reduced inflammation.

DP_1 and DP_2 in Dendritic Cells

DP_1 and DP_2 are both expressed on murine dendritic cells[29,30]. A role for PGD_2-mediated signaling in dendritic cells was first discovered through studies of a murine parasitic infection model. In mice, percutaneous infection with the helminth *Schistosoma mansoni* led to retention of Langerhans cells (LC), specialized antigen-presenting cells, within the epidermis, rather than migration to the skin-draining lymph nodes as would normally occur after infection. It was found that helminth infection led to PGD_2 production in the skin and retention of LCs within the skin through DP_1 receptor activation[29]. Further studies showed that *S. mansoni* produces PGD_2 through the parasitic enzyme Sm28GST, which shares 32% homology with hematopoietic-type PGD synthase[31], implying that parasite generation of PGD_2 and subsequent inhibition of dendritic cell migration through DP_1 activation evolved as a means for parasites to evade the immune system. Indeed, DP_1-deficient mice exhibited disappearance of LC from the epidermis and decreased worm and egg burden after infection, demonstrating that this parasitic evasion process is thwarted in the absence of DP_1 signaling[31].

Subsequently, similar roles for DP_1 regulation of dendritic cells have been found in other inflammation models. In a mouse contact hypersensitivity model, pretreatment with the DP_1 agonist BW24C leads to decreased ear swelling and epidermal LC retention, rather than migration to the skin-draining lymph nodes, after topical FITC application[29]. Similarly, in an OVA-induced model of atopic dermatitis, DP_1 activation results in increased LC epidermal retention and decreased numbers of activated OVA-specific T cells in affected skin, with resultant decreases in epidermal swelling[32]. Cytokine and chemokine analysis of the skin showed that DP_1 activation leads to a down-regulation of Th2-associated markers (IL-4, CCL11/eotaxin-1, CCL22/MDC, CCL17/TARC, CCR3, and CCR4) along with increased levels of Th1-associated markers (IFN-γ, CXCL10/IP-10, CXCR3, and CCR5)[32]. In the lung, DP_1, but not DP_2, activation leads to decreased lung dendritic cell migration to the thoracic lymph nodes after intratracheal instillation of FITC-OVA, as well as decreased lymph node T-cell proliferation and IL-4, IL-10, and IFN-γ production[33].

Although mRNA for both DP_1 and DP_2 are found in human dendritic cells, flow cytometry analysis demonstrates significant expression of only DP_1 on both immature and mature DCs[8]. Both TNF-induced migration of LCs *in vitro* and chemotaxis to CCL20/MIP-3α and CCL19/ELC are inhibited by

DP_1 activation, without altering expression levels of their receptors CCR6 and CCR7[32]. Similarly, PGD_2 and the DP_1 agonist BW245C inhibit CCL5/RANTES- and CCL19/ELC-induced chemotaxis of monocyte-derived DCs (MoDCs). Unlike LCs, incubation of MoDCs in the presence of PGD_2 alters their expression of cell surface markers and costimulatory molecules, notably decreasing CCR7 and subsequent ability to migrate towards CCL19/ELC[8,34]. PGD_2 treatment of MoDCs also impacts their cytokine expression profile, consistently suppressing levels of secreted Th1-related factors IL-12 and CXCL10/IP-10 and enhancing IL-10 production, while more variably affecting Th2-related chemokine expression[8,34]. MoDCs differentiated in the presence of PGD_2 have a diminished ability to promote allergen-induced T-cell proliferation, but favor the production of Th2 cells over Th1 cells *in vivo*[8,34]. These functions are replicated in part by selective DP_1 agonism with BW245C and not reproduced with DP_2 agonist, but some functions such as alteration of cell surface markers appear to be induced by PGD_2 alone, implying that PGD_2 may also affect DCs in a DP_1-independent manner. Collectively, these data indicate a role for PGD_2/DP_1 in suppressing the migration of DCs out of tissues to the draining lymph nodes and in favoring Th2 responses.

THE LTB_4 RECEPTORS BLT_1 AND BLT_2

Leukotriene B_4 (LTB_4) has been known to induce numerous inflammatory functions in leukocytes, including chemotaxis, degranulation, and adhesion to endothelial surfaces. BLT_1, the first described LTB_4 receptor, was identified using a cDNA subtraction method in retinoic acid–differentiated HL-60 human leukemia cells[35], with the mouse ortholog being independently identified soon afterwards[36]. BLT_1 is a seven-pass transmembrane G-protein coupled receptor with 78% homology at the amino acid level in both the human and mouse forms[37], implying conserved functions across the two species. BLT_1 binds LTB_4 with high affinity, with K_d ranging from 0.39 to 1.5 n*M* in human neutrophils and transfected CHO and HEK cells[37], and high specificity, as competitive binding studies show displacement only with 20-hydroxy LTB_4 and 12-epi LTB_4[38]. Initial Northern blotting studies of human tissues displayed highest BLT_1 expression in peripheral blood leukocytes, with lower expression in the spleen and thymus[35]. Protein expression of BLT_1 on resting human peripheral blood leukocytes has since been demonstrated on granulocytes, monocytes, CD4 and CD8 lymphocytes, $CD19^+$ B cells[39,40,41], as well as on transformed cells, such as certain B-cell leukemia clones[40] and the Jurkat T-cell and HMC-1 mast cell lines[42]. Northern blotting of mouse tissues revealed similar BLT_1 expression in IL-5–treated eosinophils, T-cell lymphomas, and activated macrophages and neutrophils, as well as low levels in the lung, lymph nodes, and spleen[43]. While BLT_1 expression has been classically restricted to leukocytes, it has recently been described in human endothelial cells[44], and human and mouse vascular smooth muscle cells[45,46] with BLT_1 activation resulting in cell migration, proliferation, and chemokine production that contribute to enhanced atherogenic and inflammatory responses (Table 2).

Previous studies had suggested that there existed two separate LTB_4 receptors on neutrophils, one binding LTB_4 with high affinity and the other binding with lower affinity, with each receptor postulated as mediating separate functions, such as chemotaxis and degranulation[47]. Indeed, a second low-affinity LTB_4 receptor, designated BLT_2, was identified in humans and mice based on identification of an open reading frame encoding a seven transmembrane-spanning receptor with sequence similarities to BLT_1[48], which was independently identified and cloned by other groups[49,50,51]. HEK cells transfected with human BLT_2 bind LTB_4 with a K_d of 23 n*M*, which is 20 times higher than that of human BLT_1[38]. Human BLT_2 also binds and is activated by a broader range of eicosanoids, including 20-hydroxy LTB_4, 12-epi-LTB_4, 12(S)- and 15(S)-hydroxyeicosatetraenoic acid (HETE), and 12(S)- and 15(S)-hydroperxyeicosatetraenoic acid

TABLE 2
BLT_1 and BLT_2 Receptors

	BLT_1	BLT_2
Receptor expression on leukocytes	*Human*: neutrophils, eosinophils, basophils, mast cells, monocytes, CD4 and CD8 cells	*Human*: neutrophils, eosinophils, monocytes, HMC-1 cells (mast cell line), dendritic cells
	Mouse: neutrophils, eosinophils, mast cells, monocytes, dendritic cells, activated Th1 and Th2 cells, effector CD8 cells	*Mouse*: mast cells
Agonists	LTB_4, 12-epi-LTB_4	LTB_4, 12-epi-LTB_4, 12(S)-HETE, 12(S)-HPETE, 12(R)-HETE, 20-hydroxy-LTB_4
Antagonists	CP105696 ZK158252 CP195543 U75302 ONO4057	LY255283 ZK158252 CP195543

(HPETE)[38]. CHO cells transfected with human BLT_2 and stimulated with LTB_4 demonstrate calcium flux and chemotaxis inhibitable by pertussis toxin[38,48], indicating function as a classical chemoattractant receptor.

Human BLT_2 shares 45.2 and 44.6% homology at the amino acid level with human and mouse BLT_1, respectively, while human and mouse BLT_2 share an even higher degree of homology at 92.7%[48]. Interestingly, the open reading frame of human BLT_2 overlaps with the putative promoter region of the BLT_1 gene[52], initially suggesting that transcription of the two receptors may be linked. However, BLT_1 expression is largely limited to leukocytes, while human BLT_2 is ubiquitously expressed in various tissues, with high levels in the spleen, liver, leukocytes, ovary, testes, pancreas, and heart[48,49,50,51]. At the RNA level, human BLT_2 is found in resting CD4, CD8, CD19, and CD14 cells[53]. In spite of significant shared homology, mouse BLT_2 differs significantly from human BLT_2 in that it is not ubiquitously expressed, but rather has a more restricted distribution in the small intestine, colon, and keratinocytes[54] (Table 2).

BLT_1 and Neutrophils

LTB_4 was first recognized as a potent stimulator of neutrophil chemotaxis and aggregation. Since then, multiple roles for LTB_4-mediated neutrophil effects have been described, including increased expression of surface neutrophil CD11/CD18 leading to enhanced adhesion to endothelial surfaces[55], induction of granular content release, generation of reactive oxygen species, and retardation of apoptosis[56]. In human cells, BLT_1 was first identified on granulocyte-like differentiated HL-60 cells[35], and protein expression was later confirmed using BLT_1-specific monoclonal antibodies[57] and presumed to mediate known LTB_4 effects on neutrophils. Some uncertainty remains as to the presence of BLT_2 in human neutrophils, as some studies demonstrated its presence using quantitative PCR[49] and flow cytometry[43], while a more recent study did not find significant message for BLT_2[58].

Mice overexpressing the human BLT_1 receptor demonstrate enhanced neutrophil migration in models of LTB_4-induced skin inflammation and ischemia perfusion[59]. *In vitro* studies utilizing the BLT_1-specific inhibitor CP-105,696 have demonstrated that LTB_4 activation of human neutrophils are mediated through BLT_1, including calcium flux, chemotaxis, CD11b up-regulation, and retardation of apoptosis[60,61]. However, BLT_1 inhibition using U75302 demonstrates residual calcium flux and degranulation when human neutrophils are similarly stimulated with LTB_4, suggesting some BLT_2

involvement in these processes[43]. Treatment of human peripheral neutrophils with dexamethasone enhances BLT_1 expression, as well as calcium flux, chemotaxis, and survival[62]. Treatment with both the BLT_1 inhibitor U75302 and BLT_2 inhibitor LY255283 blocks these effects[62], implying that endogenous production of LTB_4 is critical for these dexamethasone-mediated effects and suggesting an active role for both BLT_1 and BLT_2 on neutrophil function. Stimulation by other mediators may also lead to activation of neutrophil LTB_4 synthesis and autocrine activation, as PAF-induced neutrophil degranulation and chemotaxis are both reduced by inhibition of 5-lipoxygenase activating protein (FLAP) and BLT_1[63].

CP-105,696 is also a functional specific inhibitor of murine BLT_1[64] and has been used to probe BLT_1 function in mouse models of inflammation. Administration of this inhibitor in a mouse cremasteric venule model of inflammation decreases neutrophil adhesion to and transmigration through IL-1β–stimulated endothelium[65], suggesting a role for BLT_1 in neutrophil extravasation. CP-105,696 also reduces neutrophil migration in an LTB_4-mediated model of skin inflammation[66] and synovial neutrophil infiltration in autoantibody-induced inflammatory arthritis[67]. In a model of sublethal cecal puncture, treatment of mice with CP-105,696 reduces neutrophil migration into the peritoneal cavity with subsequent increased bacterial loads and increased mortality[68]. In a rat model of renal ischemia-reperfusion injury, ONO-4057, a BLT_1/BLT_2 inhibitor, preserves renal function and reduced kidney neutrophil infiltration and structural damage[69].

The generation of $BLT_1^{-/-}$ mice has also highlighted the necessity for BLT_1 in directing neutrophil migration in numerous inflammatory responses. Initial characterization of neutrophils isolated from $BLT_1^{-/-}$ mice displayed eradication of calcium flux, chemotaxis[70,71], and degranulation[72] in response to LTB_4, as well as decreased early neutrophil recruitment in zymosan-induced peritonitis[71]. In an OVA-induced model of asthma, there are reduced numbers of neutrophils in the BAL after early antigen challenge in $BLT_1^{-/-}$ mice compared with wild-type, and $BLT_1^{-/-}$ mice also display diminished neutrophil recruitment in the airways after administration of OVA-IgG1 and OVA-IgE complexes[73]. In an autoantibody-induced model of inflammatory arthritis, $BLT_1^{-/-}$ mice are resistant to the development of arthritis, but adoptive transfer of wild-type neutrophils into these mice restores the arthritic response, a finding also replicated by transferring wild-type neutrophils into 5-LO–deficient mice that cannot generate LTB_4[67,74]. These studies show that autocrine activation of BLT_1 on neutrophils is required for BLT_1-deficient neutrophils to be recruited into the joint subsequently, indicating a novel mechanism of autocrine BLT_1-mediated neutrophil activation in the amplification of innate immune responses.

BLT_1 and Eosinophils

LTB_4 has numerous stimulatory effects on eosinophils, including the induction of chemotaxis, aggregation[75], degranulation[76], and respiratory burst[77], although it does not have any effect on eosinophil apoptosis *in vitro*[61]. Since then, both BLT_1 and BLT_2 mRNA have been detected in human eosinophils[49], indicating that either of these receptors may mediate these actions. CP-105,696–mediated BLT_1 inhibition diminishes LTB_4-induced calcium flux in human eosinophils[61]; however, further detailed studies of the differential roles of BLT_1 and BLT_2 activation on human eosinophil chemotaxis, aggregation, and degranulation have not yet been described in the literature. Of note, basophils also express BLT_1, but not BLT_2, and IL-3-primed basophils degranulate upon exposure to LTB_4[58].

Murine BLT_1 was first identified using degenerate PCR amplification of eosinophil mRNA with human BLT_1 expression being confirmed on human eosinophils[36], and accordingly, abrogation of BLT_1 function has been shown to lead to attenuated eosinophil migration in various mouse models of inflammation. $BLT_1^{-/-}$ mice have preferentially decreased eosinophil recruitment in thioglycollate-induced peritonitis[70] and in early antigen challenge in OVA-induced asthma[73]. In addition, administration of CP-105,696 reduces eosinophil infiltration of the spinal cord after induction of experimental allergic encephalomyelitis (EAE)[78]. CP-105,696 diminishes eosinophil recruitment in models of stem cell factor (SCF)- and OVA-induced pleurisy in mice[79]. It was thought that SCF

stimulates mast cells to produce LTB_4, leading to subsequent eosinophil BLT_1-mediated migration. However, eosinophil recruitment after direct injection of CCL11/eotaxin-1 into the pleural space is also diminished by BLT_1 inhibition, although the CCL11/eotaxin-1 injection itself does not increase pleural LTB_4 levels[80], leading the authors to postulate that CCL11/eotaxin-1 induces BLT_1-LTB_4 autocrine activation of eosinophils at a microscopic level necessary for their migration towards CCL11/eotaxin-1 and possibly other chemoattractants as well.

BLT_1 and BLT_2 and Mast Cells

An analysis of mast cell–derived factors that induce chemotaxis of immature murine bone marrow–derived mast cells (BMMCs) identified LTB_4 as the active chemotactic agent[81]. However, as they mature in SCF, both murine BMMCs and human cord blood–derived mast cells lose their ability to migrate towards LTB_4[81], suggesting a mechanism by which mature mast cells recruit their progenitors from the bone marrow to tissue sites to maintain their presence in the periphery. In this study, levels of BLT_1 mRNA decreased with murine mast cell maturation and were presumed to be the cause for decreased ability to migrate towards LTB_4, but the specific LTB_4 receptor responsible for mast cell chemotaxis was not confirmed through the use of pharmacologic inhibitors. Another study has subsequently demonstrated message for both BLT_1 and BLT_2 in murine BMMCs and the human mast cell line HMC-1[42]. Increasing the time of incubation in SCF diminishes human mast cell BLT_1 surface expression, suggesting an explanation for the loss of migration to LTB_4 during the maturation of murine BMMCs. However, chemotaxis of both murine BMMCs and HMC-1 cells towards LTB_4 is reduced with either BLT_1 or BLT_2 inhibition[42], indicating that both these receptors are capable of inducing chemotaxis in mast cells. Although the physiologic significance of this dual receptor usage on mast cells is not yet known, LTB_4 clearly has the potential of contributing to allergic and inflammatory responses by recruiting mast cells to tissue sites during inflammation and maintaining tissue mast cell homeostasis after preexisting mast cells have released their granular contents.

BLT_1 and Monocytes

LTB_4 has been shown to activate monocytes and macrophages by inducing chemotaxis, surface CD11b expression, and phagocytosis. Message for both BLT_1 and BLT_2 receptors has been detected in $CD14^+$ monocytes[53], and flow cytometric studies of human peripheral blood leukocytes have confirmed BLT_1 expression on $CD14^{++}CD16^-$ monocytes, which represent 85–90% of the peripheral monocyte population[82]. Both BLT_1 expression and activity are decreased by the addition of inflammatory cytokines such as IFN-γ and TNF, while BLT_1 transcription is elevated by IL-10 and dexamethasone[82]. BLT_1^+ monocytes also express increased levels of CCR2, a chemokine receptor whose expression is also regulated similarly to BLT_1, implying a cooperative role for BLT_1- and CCR2-mediated signaling and chemotaxis in this inflammatory monocyte subset. Additionally, BLT_1-activated monocytes produce CCL2/MCP-1[83]. These data suggest that BLT_1-stimulated monocytes may amplify further monocyte recruitment by generating CCL2/MCP-1 and promoting subsequent CCR2-mediated chemotaxis.

In mice, BLT_1 and CCR2 signaling on monocytes also appear to be linked. In a cecal ligation and puncture (CLP) model of septic peritonitis, CCL2/MCP-1 blockade reduces neutrophil and macrophage infiltration and LTB_4 production; however, BLT_1 inhibition with CP-105,696 also reduces neutrophil and macrophage infiltration and CCL2/MCP-1 production, demonstrating cross-talk between the two chemoattractants in inducing inflammatory responses to infection, as inhibition of either CCL2/MCP-1 or BLT_1 significantly decreased mouse survival[84]. CP-105,696 also inhibits monocytic foam cell migration and CD11b expression in a atherosclerosis model[85], and nitric oxide production in *Trypanosoma cruzi*-infected macrophages[86].

BLT_1 and T Lymphocytes

Although LTB_4 is characteristically identified as a potent activator of leukocytes of the innate immune system, such as granulocytes and monocytes, LTB_4 has been previously shown to bind to T cells[87] and induce T-cell chemotaxis *in vitro*[88], as well as T-cell cytokine production[37]. Characterization of the BLT_1 receptor led to an exploration of its expression on human peripheral blood leukocytes and its identification on T cells[39,53]. BLT_1 is also expressed in murine T-cell lymphomas[36], suggesting that it may be expressed on peripheral blood T cells in mice as well.

Exploration of the functional roles of BLT_1 on T cells using mouse models of inflammation has revealed that BLT_1 activation plays a critical role in the recruitment of effector CD4 and CD8 cells early in inflammation. Although BLT_1 is not found in naïve T cells, BLT_1 expression is significantly up-regulated in activated CD4 Th1 and Th2 cells[89], and effector CD8+ cells[90,91]. In the early phases of an active immunization asthma model, $BLT_1^{-/-}$ mice exhibit defective recruitment of CD4 and CD8 cells in the airways, but have normal levels of airway T cells in an adoptive transfer model, indicating an important role for BLT_1-mediated T-cell trafficking in both humoral and adaptive immune responses[89]. Peribronchial lymph node cells from OVA-sensitized $BLT_1^{-/-}$ mice have impaired Th2 cytokine (IL-5 and IL-13) production, ultimately leading to diminished airway hypersensitivity, airway and lung eosinophilia, goblet cell hyperplasia, and IgE production after OVA inhalation[72]. These studies demonstrate that BLT_1 activation of helper T cells is a critical component of the early allergic response.

Effector CD8 cells also display significantly higher levels of BLT_1 expression compared with central memory CD8 cells and migrate in response to LTB_4 *in vitro* and *in vivo* settings[90,91]. Analysis of mast cell supernatants identify LTB_4 to be the major mast cell–produced chemotactic factor inducing effector CD8 T cell migration[91], and that mast cell- and $Fc\varepsilon RI^{-/-}$ mice produce lower levels of LTB_4 in BAL fluid after OVA sensitization and challenge[92]. Transfer of OVA-primed $BLT_1^{-/-}$ effector CD8 T cells into sensitized $CD8^{-/-}$ mice fails to restore airway hyper-responsiveness (AHR), eosinophilic inflammation, and IL-13 production both in an adoptive transfer and a mast-cell dependent model of allergic airway disease[92,93]. Collectively, these studies place an important role for BLT_1 activation of T cells on the generation of allergic airway disease, both in the induction of Th2 cell responses with IgE and cytokine production, and in T_{EFF} recruitment and activation, providing a critical transition between the initial rapid innate immune responses towards the development and propagation of adaptive immunity.

Other clinically relevant, T-cell–mediated inflammatory processes are dependent on BLT_1. BLT_1 blockade with CP-105,696 in a murine heterotopic cardiac transplantation model increases allograft survival with diminished T lymphocyte, granulocyte, and macrophage tissue infiltration into affected organs[94]. In a murine acute lung rejection model, adoptive transfer of lung-specific $BLT_1^{-/-}$ CD8 effector cells results in diminished lung inflammation and increased mouse survival, and $BLT_1^{-/-}$ mice that undergo tracheal transplants display significantly less fibroproliferation and airways hyper-responsiveness, along with defective T-cell recruitment[95]. In a mouse model of autoimmune uveitis, adoptive T-cell transfer of antigen-specific $BLT_1^{-/-}$ T cells results in less severe disease than transfer of T cells from wild-type mice, although there appears to be a BLT_1-dependent contribution to the recruitment of other immune cells such as neutrophils[96].

A detailed characterization of BLT_1 in human resting peripheral blood cells has identified BLT_1 expression on a rare subset of $CD3^+CD4^+$ and $CD3^+CD8^+$ cells (0–1%)[41]. This BLT_1^+ population is enriched for late activation markers CD38 and HLA-DR and inflammatory chemokine receptors, and they tend to express more polarizing cytokines. However, dendritic cell stimulation of CD4 and CD8 cells may lead to a dramatic increase in surface BLT_1 expression. Asymptomatic atopic asthmatics demonstrate increased numbers of BLT_1^+ CD4 and CD8 memory T cells in the airways, and EBV-specific CD8 cells from acutely infected individuals also have increased levels of BLT_1 expression compared with those with asymptomatic chronic infection[41]. In addition, patients with bronchiolitis obliterans post lung transplantation express greater numbers of BLT_1^+ CD4 and CD8 cells in the airways compared with normal transplanted lungs[95]. These studies demonstrate that BLT_1 is constitutively expressed on antigen-primed memory/effector T cells whose phenotype suggests a primary function of responding

rapidly to inflammatory stimuli. In the setting of infection or T-cell activation, however, BLT_1 expression is transiently increased on this T-cell subpopulation, enhancing their ability to quickly respond to the early phases of infectious and inflammatory processes.

BLT_1 and BLT_2 and Dendritic Cells

Murine bone marrow–derived dendritic cells (mBMDCs) migrate in response to LTB_4, an effect abrogated in cells lacking BLT_1[97]. In addition, LTB_4 up-regulates expression of CCR7 and its ligand CCL19/ELC, both of which mediate mBMDC migration to the draining lymph nodes. Accordingly, $BLT_1^{-/-}/BLT_2^{-/-}$ double deficient mice develop diminished dendritic cell migration to the lymph node, and ear inflammation and swelling in a model of contact hypersensitivity[97]. These data indicate that BLT_1 activation of murine dendritic cells contributes to the inflammatory response by enhancing their migration via CCR7 and its ligands to the draining lymph nodes, where they encounter and activate antigen-specific cells. Human monocyte-derived dendritic cells also migrate towards LTB_4 in a PTX-sensitive fashion. However, these cells have been shown to express BLT_2 message and chemotaxis is eliminated by the BLT_2-specific inhibitor LY255283[98]. These studies confirm an active biological role for LTB_4 activation in dendritic cell function, although it appears in these initial studies that there may be differences in receptor usage between species, which need to be further defined.

THE CYSTEINYL LEUKOTRIENE RECEPTORS $CYSLT_1$ AND $CYSLT_2$

The cysteinyl leukotrienes (cysLTs), LTC_4, LTD_4, and LTE_4, are rapidly synthesized by macrophages, mast cells, eosinophils, and basophils, and induce critical components of the allergic response, including bronchial smooth muscle constriction, vascular permeability, and leukocyte activation[99]. The cysLTs mediate their actions through two receptors, $CysLT_1$ and $CysLT_2$, both seven transmembrane-spanning G-protein receptors. Human $CysLT_1$ was independently cloned and characterized by two groups[100,101]. $CysLT_1$ binds preferentially to LTD_4, with 200-fold less affinity for LTE_4 and LTC_4, and cellular calcium mobilization by $CysLT_1$ is not affected by PTX treatment. However, previous studies with THP-1 cells have suggested that while calcium flux is mediated by a PTX-insensitive signaling pathway, chemotaxis is mediated through a separate, PTX-sensitive mechanism[102]. Northern blot analysis detects $CysLT_1$ message rather ubiquitously in human organ tissues, with highest expression in the spleen and peripheral blood leukocytes, followed by the lung, placenta, and intestine, with detectable transcript in the promyelocytic cell line HL-60 and the lymphocytic leukemia cell line U937[100,101]. *In situ* hybridization studies have demonstrated human $CysLT_1$ in lung smooth muscle and macrophages, eosinophils, monocytes, and B cells[103], and $CysLT_1$ message and signaling are present in human mast cells derived from cord blood as well[104]. $CD34^+$ hematopoietic progenitor cells also express $CysLT_1$ and migrate in response to LTD_4[105]. Transgenic mice overexpressing human $CysLT_1$ develop enhanced airway eosinophilia, Th2 cytokine production, and airways hyper-responsiveness in a model of *Aspergillus fumigatus* sensitization and challenge[106]. Mouse $CysLT_1$ bears 87% homology with the human ortholog at the amino acid level and shares similar binding characteristics[107,108,109]. Mice express $CysLT_1$ at high levels in the skin, lung, macrophage, and small intestine, although some strain difference exists with more intense skin expression in C57Bl/6 mice compared with the 129+Ter/Sv strain[109]. Detailed *in situ* hybridization of 129+Ter/Sv mouse skin reveals $CysLT_1$ in subcutaneous connective tissue fibroblasts[109] (Table 3). $CysLT_1$ blockade with the agents montelukast, zafirlukast, and pranlukast has significant relevance in the management of allergic respiratory diseases, as they have consistently been shown to be effective in reducing airways hyper-responsiveness and eosinophilia, and improving symptoms and quality of life in patients with asthma and allergic rhinitis[99,110].

TABLE 3
$CysLT_1$ and $CysLT_2$ Receptors

	$CysLT_1$	$CysLT_2$
Receptor expression on leukocytes	*Human*: eosinophils, basophils, mast cells, monocytes and macrophages, dendritic cells, B cells, T cells	*Human*: eosinophils, mast cells, macrophages, dendritic cells, T cells
	Mouse: macrophages	*Mouse*: macrophages
Agonists	LTD_4, LTC_4, LTE_4	LTC_4, LTD_4, LTE_4
Antagonists	Montelukast (MK476) Zafirlukast (ICI204219) Pranlukast (ONO1078) MK571 BAYu9773 LY171833	BAYu9773 (partial agonist)

Human $CysLT_2$ shares 38% amino acid homology with human $CysLT_1$, and binds LTC_4 and LTD_4 with equal affinity, followed by LTE_4[111,112,113]. Northern Blot and dot blot analysis has detected high levels of human $CysLT_2$ in the heart, spleen, peripheral blood leukocytes, placenta, and adrenal glands, while *in situ* hybridization demonstrates expression in lung smooth muscle cells, adrenal medulla, and cardiac Purkinje fibers[111,112,113]. In addition, $CysLT_2$ message has been identified in HUVECs, levels of which are elevated on IL-4 stimulation or upon reaching confluence[114]. Among leukocytes, human $CysLT_2$ is expressed on macrophages, eosinophils[111], and mast cells[115]. Mouse $CysLT_2$ shares 73% sequence homology with human $CysLT_2$ and 39% homology with mouse $CysLT_1$, and binds to the same natural ligands as human $CysLT_2$ with similar affinities[109,116]. Mouse $CysLT_2$ transcript is more ubiquitously distributed, including brain, lung, spleen, small intestine, kidney, skin, adrenals, thymus, and spinal cord, while cellular expression has been described in macrophages and subcutaneous fibroblasts[109,116] (Table 3).

$CysLT_1$ and Eosinophils

The presence of CysLTs in allergic and atopic conditions characterized by eosinophilic inflammation suggests that they may play a direct role in inducing eosinophil activation and migration. Mice deficient in LTC_4 synthase, the enzyme required for CysLT synthesis, have markedly decreased eosinophilic inflammation in an asthma model[117], and selective $CysLT_1$ inhibition reduces tissue eosinophilia in both murine[118] and human allergic conditions. *In vitro* studies have shown that LTC_4, LTD_4, and LTE_4 induce surface expression of the adhesion molecule Mac-1 (but not LFA-1) and chemotaxis of human peripheral blood eosinophils in a $CysLT_1$-dependent manner[119,120]. $CysLT_1$ inhibition also diminishes eosinophil migration across endothelial cell layers in a static *in vitro* model[121]. These studies suggest that one mechanism by which CysLTs contribute to eosinophilic inflammation is by directly recruiting eosinophils from the circulation into target organs.

However, other proinflammatory effects of $CysLT_1$ activation on eosinophils include promotion of their survival and effector functions. LTD_4 enhances eosinophil differentiation from progenitor cells[122] and promotes mature eosinophil survival[123], of which both processes are $CysLT_1$ dependent. CysLTs also induce eosinophil granule release. In a murine asthma model, montelukast inhibits eosinophil degranulation in lung tissues[118]. Eosinophils differentiated *in vitro* from human cord blood release preformed IL-4 after CysLT stimulation in a dose- and PTX-dependent manner, a process blocked by $CysLT_1$ inhibition[124]. When peripheral blood eosinophils are used, however, LTC_4 and LTD_4 elicit IL-4 release when added to permeabilized eosinophils only, while addition of $CysLT_1$ and $CysLT_2$ inhibitors

does not block this release. These findings suggest that in addition to binding $CysLT_1$, CysLTs may bind novel CysLT intracellular receptors necessary for the transcription and release of inflammatory cytokines[125].

$CysLT_1$ and Monocytes/Macrophages

Initial characterization of the human $CysLT_1$ receptor revealed prominent staining in pulmonary macrophages[103], suggesting a potential important role for CysLT activation of the monocyte/macrophage lineage in allergic airway disease. In a rat alveolar macrophage cell line NR8383, combined treatment with LTD_4 and lipopolysaccharide (LPS) significantly increases macrophage production of CCL3/MIP-1α, a chemoattractant for eosinophils and monocytes, a response reversible by $CysLT_1$ inhibition[126]. In this fashion, CysLT activation of macrophages serves as an additional means of inducing eosinophilic inflammation. Of interest is that both LTD_4 and LPS were required for this response, implicating a role for Toll-like receptors in the initiation of allergic responses predominated by CysLTs.

Message for $CysLT_1$ is found in resting human monocytes and macrophages, as well as the monocytic cell line THP-1. Incubation with the Th2-like cytokines IL-4 and IL-13 further increases $CysLT_1$ transcription, surface expression, and chemotaxis towards LTD_4, overall enhancing monocyte participation in the allergic response[127]. IL-4 stimulation of THP-1 cells induces $CysLT_1$ expression mediated by STAT6 activation, leading to the enhanced production of CCL2/MCP-1[128]. In addition to mediating monocyte chemotaxis towards CysLTs directly, $CysLT_1$ may enhance their chemotaxis towards other chemoattractants. Addition of zafirlukast or montelukast to THP-1 cells or human monocytes reduces chemotaxis and calcium flux in response towards CCL2/MCP-1 through a p38-MAPK pathway, without altering their production of LTB_4 or LTD_4[129]. These data suggest that $CysLT_1$ activation of monocytes amplifies Th2-mediated responses, in which Th2 cytokines induce enhanced monocyte responsiveness to LTD_4 and promote the recruitment of monocytes and eosinophils towards sites of inflammation.

$CysLT_1$ and $CysLT_2$ and Mast Cells

Mast cells are an integral component of allergic and inflammatory responses, and produce CysLTs on stimulation with IL-4 or FcεRI cross-linking. Both $CysLT_1$ and $CysLT_2$ have been identified in cord blood–derived human mast cells and the human mast cell line HMC-1[115,130,131]. $CysLT_1$ activation increases human and mouse mast cell proliferation in the presence of IL-4[132]. Unprimed human mast cells respond to LTC_4 and LTD_4 as demonstrated by calcium mobilization, a process primarily mediated through $CysLT_1$. LTC_4 and LTD_4 also amplify the transcription and release of IL-5, TNF-α, and CCL4/MIP-1β through ERK- and NFAT/calcineurin-mediated $CysLT_1$ activation of IL-4-primed mast cells. Mast cell cytokine production resulting from IgE cross-linking of FcεRI is also partially dependent on autocrine production of CysLTs and subsequent activation of $CysLT_1$. However, mast cell degranulation and production of histamine and PGD_2 is not affected by $CysLT_1$ activation[104]. These studies show a role for $CysLT_1$ activation of mast cells in amplifying Th2 inflammation primarily through activating the transcription and release of cytokines and chemokines, rather than inducing immediate degranulation.

A GenBank search for sequences homologous with $CysLT_1$ and $CysLT_2$ revealed that these receptors share 24–32% homology with the purinergic (P2Y) receptor family, and in particular, with the P2Y6 receptor, which preferentially binds the pyrimidinergic ligand UDP. Indeed, mast cell $CysLT_1$ also acts as an active receptor for UDP, as shown by initiation of calcium flux that is blocked by the $CysLT_1$ inhibitor MK571[130]. UDP activation of $CysLT_1$ strongly induces the production of TNF-α and CCL4/MIP-1β in

IL-4–primed mast cells in a manner similar to LTD_4 and LTE_4, but it induces IL-5 less strongly than the CysLTs[104].

Priming of mast cells with IL-4 prior to $CysLT_1$ stimulation increases calcium mobilization, but it does not affect $CysLT_1$ receptor cell surface expression[130]. $CysLT_2$ receptor expression is increased after IL-4 priming, however, accounting for this difference and indicating that this is a functional receptor on mast cells. $CysLT_2$ regulation and signaling on mast cells also differs from $CysLT_1$ in other ways. Stimulation with LTC_4 and LTD_4 in the presence of $CysLT_1$ inhibitor suppresses the production of most cytokines, with the exception of CCL2/MCP-1 and CXCL8/IL-8, indicating that these are induced by $CysLT_2$ activation alone. Unlike $CysLT_1$, which has been shown to signal through PTX-insensitive pathways, PTX completely blocks $CysLT_2$-mediated CXCL8/IL-8 production, a neutrophil-active chemokine[115]. Therefore, $CysLT_2$ may play a role in innate immune responses by activating mast cell production of a distinct set of chemokines.

$CysLT_1$ and Dendritic Cells

An early study demonstrated a direct role for CysLTs in controlling dendritic cell migration through studies of multidrug resistance associated protein 1 (MRP1, also known as Abcc1), which is required for CysLT transport outside of the cell[133]. In a skin inflammation model, dendritic cells of MRP1/$Abcc1^{-/-}$ mice are retained in the epidermis and dermis with diminished migration to the draining lymph nodes. In addition, chemotaxis towards CCL19/ELC is dramatically decreased by 90% in MRP1/$Abcc1^{-/-}$ bone marrow–derived dendritic cells, with 35% reduction in chemotaxis to CCL21/SLC. Administration of exogenous LTD_4 either *in vivo* or *in vitro* reinstates the dendritic cell chemotactic response, indicating that dendritic cells must synthesize LTD_4 and export it out of the cell, where it binds to $CysLT_1$ receptor in an autocrine manner and induces migration towards CCL19/ELC.

$CysLT_1$ and $CysLT_2$ receptors have subsequently been identified on human MoDCs, although *in vitro* differentiation and maturation results in a relative down-regulation of CysLT receptor expression with resultant reduced response to LTD_4 as manifested by decreased calcium flux and chemotaxis[134]. $CysLT_1$ antagonism has been shown to have significant effects on dendritic cell localization in the early asthma response, as pranlukast-treated patients have fewer circulating myeloid $CD33^+$ DCs compared with placebo-treated controls, although there are no differences in the number of circulating plasmacytoid $CD123^+$ DCs[135]. This difference may be accounted for by the fact that myeloid DCs express higher levels of $CysLT_1$ than plasmacytoid dendritic cells and would be affected more by $CysLT_1$ inhibition[135], but this decrease in circulating myeloid DCs after pranlukast treatment does not definitively indicate between which compartments dendritic cell migration route is interrupted. $CysLT_1$ activation of DCs also induces cytokine production, particularly of the Th2 type. Upon allergen stimulation, MoDCs from atopic patients produce more IL-10 and TNF-α, and induce CD4 cells to produce more IL-5 and IFN-γ when compared with MoDCs from nonatopic controls, processes which are inhibited by pranlukast and montelukast[136]. $CysLT_1$ stimulation of MoDCs also induces CXCL8/IL-8 production, pointing to a role for DCs in stimulating innate immune responses as well[137].

$CysLT_1$ activation of murine dendritic cells also results in a number of proinflammatory effects. In contrast with human DCs, murine bone marrow–derived DCs express more $CysLT_1$ on stimulation with antigen, although this has been identified only at the mRNA level[138]. $CysLT_2$ expression on murine dendritic cells has not yet been described in the literature. In one study, *in vitro* stimulation of murine DCs with both CysLTs and antigen simultaneously results in both IL-10 and IL-12 production; however, while IL-10 production is suppressed by $CysLT_1$ blockade, IL-12 production is increased[138]. These findings suggest that $CysLT_1$ activation of murine dendritic cells primes the Th2 response by promoting the production of Th2-type cytokines. It is interesting to postulate that this observed increase in IL-12, a Th1 cytokine, may be due to unopposed $CysLT_2$ activation of dendritic cell and skewing towards a Th1 response, if $CysLT_2$ is eventually found to exist on these cells. Dendritic cells isolated from the spleens of OVA-sensitized mice generate both Th1 and Th2 cytokines on antigen stimulation *in vitro,* and are able to

enhance proliferation of coincubated CD4 cells, processes that are inhibited by treating the mice with pranlukast prior to isolation of dendritic cells[139].

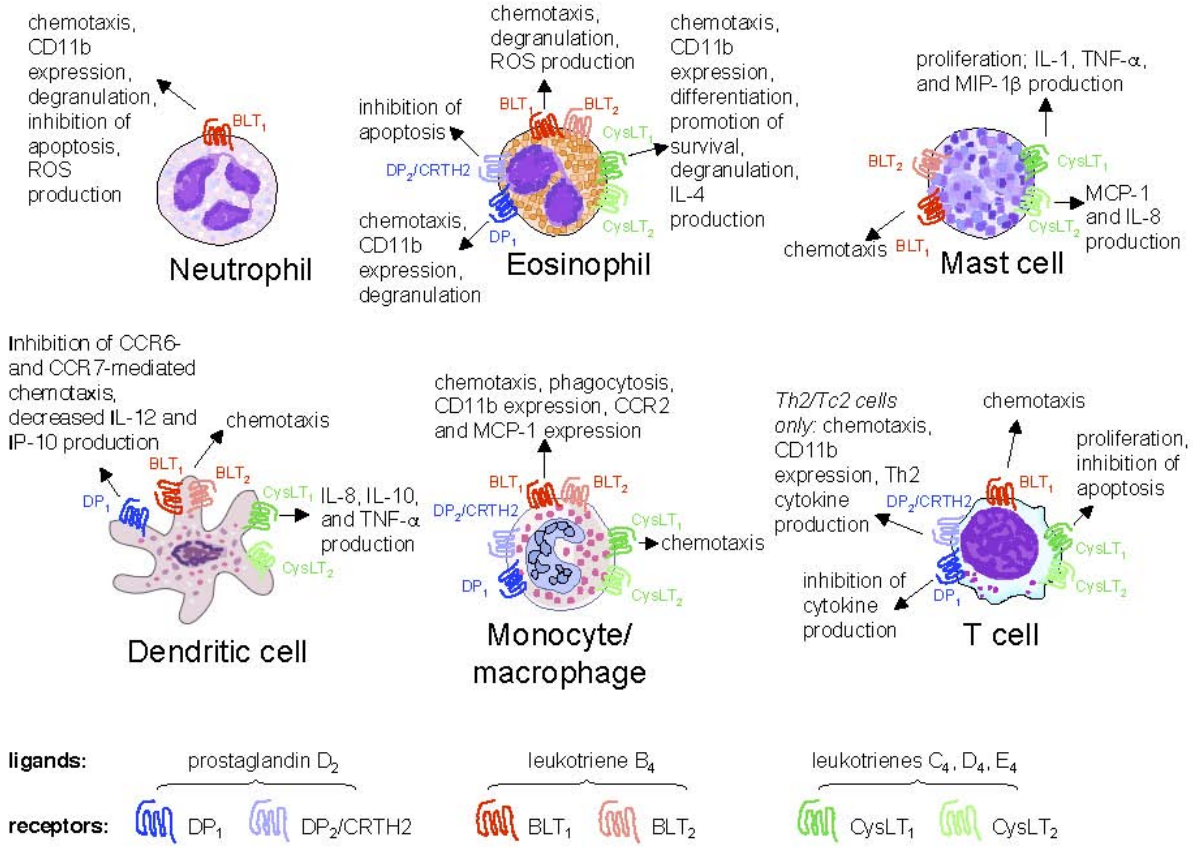

FIGURE 1. Distribution and functions of PGD_2, LTB_4, and CysLT receptors on human leukocyte populations. Leukocyte expression and known functions of DP_1, DP_2/CRTH2, BLT_1, BLT_2, $CysLT_1$, and $CysLT_2$ receptors after activation with their respective ligands are depicted. This diagram represents human leukocytes; while mouse and other species have similar distribution and functions, significant differences exist, as described in this review. ROS, reactive oxygen species.

$CysLT_1$ and Lymphocytes

Resting T cells isolated from the peripheral blood of humans[103] and mice[140] express very low levels of $CysLT_1$ and $CysLT_2$. However, murine $CysLT_1$ expression is induced in *in vitro* polarized Th1 and Th2 cells, and TCR- and CD28-activated bulk CD4 and CD8 cells, along with the ability to migrate to LTD_4[140]. One study demonstrated that only 0.7 and 2.5% of resting human T cells express $CysLT_1$ and $CysLT_2$, respectively, but incubation with IL-4 and IL-13 increases $CysLT_1$ and $CysLT_2$ expression to 9.8 and 6.9%, and anti-CD3 antibody increases expression to 78 and 65% of T cells, respectively[141]. Interestingly, incubation of CD3-activated T cells with montelukast decreases proliferation and increases the number of cells undergoing apoptosis[141], implying an important role for autocrine/paracrine activation of the $CysLT_1$ receptor in maintaining the viability of activated T cells. Studies of the CysLT

transporter MRP1/Abcc1 have provided insight into the role of CysLT signaling in murine T-cell movement[142], suggesting that autocrine/paracrine activation by T cells by CysLTs may play a role in CCR7-directed movement into lymph nodes.

Of note, one study has demonstrated that resting B lymphocytes express low levels of $CysLT_1$ and $CysLT_2$, but only $CysLT_1$ expression is increased after stimulation with IL-4 and either anti-CD40 or CD154-transfected fibroblasts. $CysLT_1$ activation by LTD_4 also results in increased IgG and IgE production and secretion, thereby providing another means of enhancing Th2-mediated stimulation[143].

SUMMARY

It has long been recognized that eicosanoids participate in critical physiological functions, such as the regulation of smooth muscle tone, vascular permeability, neuronal function, and platelet aggregation. However, many recent studies have uncovered that they have additional important roles in regulating both innate and adaptive immune responses, and the success of cysteinyl receptor blockade for the treatment of allergic and atopic conditions has demonstrated that inhibiting these pathways are viable therapeutic options for inflammatory diseases. While the numbers of eicosanoid receptors being identified on leukocyte subpopulations continues to grow, their roles in inducing specific immune responses still remain to be fully explicated (Fig. 1). The availability and development of specific eicosanoid receptor inhibitors and future studies in mice genetically deficient in these receptors will help to further characterize their diverse functions in both driving and suppressing these important immune responses.

REFERENCES

1. Brock, T.G. and Peters-Golden, M. (2007) Activation and regulation of cellular eicosanoid biosynthesis. *TheScientificWorldJOURNAL* **7**, 1273–1284.
2. Murray, J.J., Tonnel, A.B., Brash, A.R., Roberts, L.J., 2nd, Gosset, P., Workman, R., Capron, A., and Oates, J.A. (1986) Release of prostaglandin D2 into human airways during acute antigen challenge. *N. Engl. J. Med.* **315,** 800–804.
3. Barr, R.M., Koro, O., Francis, D.M., Black, A.K., Numata, T., and Greaves, M.W. (1988) The release of prostaglandin D2 from human skin in vivo and in vitro during immediate allergic reactions. *Br. J. Pharmacol.* **94,** 773–780.
4. Kabashima, K. and Narumiya, S. (2003) The DP receptor, allergic inflammation and asthma. *Prostaglandins Leukot. Essent. Fatty Acids* **69,** 187–194.
5. Boie, Y., Sawyer, N., Slipetz, D.M., Metters, K.M., and Abramovitz, M. (1995) Molecular cloning and characterization of the human prostanoid DP receptor. *J. Biol. Chem.* **270,** 18910–18916.
6. Hirata, M., Kakizuka, A., Aizawa, M., Ushikubi, F., and Narumiya, S. (1994) Molecular characterization of a mouse prostaglandin D receptor and functional expression of the cloned gene. *Proc. Natl. Acad. Sci. U. S. A.* **91,** 11192–11196.
7. Gervais, F.G., Cruz, R.P., Chateauneuf, A., Gale, S., Sawyer, N., Nantel, F., Metters, K.M., and O'Neill, G.P. (2001) Selective modulation of chemokinesis, degranulation, and apoptosis in eosinophils through the PGD2 receptors CRTH2 and DP. *J. Allergy Clin. Immunol.* **108,** 982–988.
8. Gosset, P., Bureau, F., Angeli, V., Pichavant, M., Faveeuw, C., Tonnel, A.B., and Trottein, F. (2003) Prostaglandin D2 affects the maturation of human monocyte-derived dendritic cells: consequence on the polarization of naive Th cells. *J. Immunol.* **170,** 4943–4952.
9. Tanaka, K., Hirai, H., Takano, S., Nakamura, M., and Nagata, K. (2004) Effects of prostaglandin D2 on helper T cell functions. *Biochem. Biophys. Res. Commun.* **316,** 1009–1014.
10. Spik, I., Brenuchon, C., Angeli, V., Staumont, D., Fleury, S., Capron, M., Trottein, F., and Dombrowicz, D. (2005) Activation of the prostaglandin D2 receptor DP2/CRTH2 increases allergic inflammation in mouse. *J. Immunol.* **174,** 3703–3708.
11. Matsuoka, T., Hirata, M., Tanaka, H., Takahashi, Y., Murata, T., Kabashima, K., Sugimoto, Y., Kobayashi, T., Ushikubi, F., Aze, Y., Eguchi, N., Urade, Y., Yoshida, N., Kimura, K., Mizoguchi, A., Honda, Y., Nagai, H., and Narumiya, S. (2000) Prostaglandin D2 as a mediator of allergic asthma. *Science* **287,** 2013–2017.
12. Monneret, G., Gravel, S., Diamond, M., Rokach, J., and Powell, W.S. (2001) Prostaglandin D2 is a potent chemoattractant for human eosinophils that acts via a novel DP receptor. *Blood* **98,** 1942–1948.
13. Nagata, K., Tanaka, K., Ogawa, K., Kemmotsu, K., Imai, T., Yoshie, O., Abe, H., Tada, K., Nakamura, M.,

Sugamura, K., and Takano, S. (1999) Selective expression of a novel surface molecule by human Th2 cells in vivo. *J. Immunol*. **162,** 1278–1286.

14. Hirai, H., Tanaka, K., Yoshie, O., Ogawa, K., Kenmotsu, K., Takamori, Y., Ichimasa, M., Sugamura, K., Nakamura, M., Takano, S., and Nagata, K. (2001) Prostaglandin D2 selectively induces chemotaxis in T helper type 2 cells, eosinophils, and basophils via seven-transmembrane receptor CRTH2. *J. Exp. Med*. **193,** 255–261.
15. Kostenis, E. and Ulven, T. (2006) Emerging roles of DP and CRTH2 in allergic inflammation. *Trends Mol. Med.* **12,** 148–158.
16. Nagata, K. and Hirai, H. (2003) The second PGD(2) receptor CRTH2: structure, properties, and functions in leukocytes. *Prostaglandins Leukot. Essent. Fatty Acids* **69,** 169–177.
17. Abe, H., Takeshita, T., Nagata, K., Arita, T., Endo, Y., Fujita, T., Takayama, H., Kubo, M., and Sugamura, K. (1999) Molecular cloning, chromosome mapping and characterization of the mouse CRTH2 gene, a putative member of the leukocyte chemoattractant receptor family. *Gene* **227,** 71–77.
18. Cosmi, L., Annunziato, F., Galli, M.I.G., Maggi, R.M.E., Nagata, K., and Romagnani, S. (2000) CRTH2 is the most reliable marker for the detection of circulating human type 2 Th and type 2 T cytotoxic cells in health and disease. *Eur. J. Immunol.* **30,** 2972–2979.
19. Xue, L., Gyles, S.L., Wettey, F.R., Gazi, L., Townsend, E., Hunter, M.G., and Pettipher, R. (2005) Prostaglandin D2 causes preferential induction of proinflammatory Th2 cytokine production through an action on chemoattractant receptor-like molecule expressed on Th2 cells. *J. Immunol.* **175,** 6531–6536.
20. Chevalier, E., Stock, J., Fisher, T., Dupont, M., Fric, M., Fargeau, H., Leport, M., Soler, S., Fabien, S., Pruniaux, M.P., Fink, M., Bertrand, C.P., McNeish, J., and Li, B. (2005) Cutting edge: chemoattractant receptor-homologous molecule expressed on Th2 cells plays a restricting role on IL-5 production and eosinophil recruitment. *J. Immunol.* **175,** 2056–2060.
21. Satoh, T., Moroi, R., Aritake, K., Urade, Y., Kanai, Y., Sumi, K., Yokozeki, H., Hirai, H., Nagata, K., Hara, T., Utsuyama, M., Hirokawa, K., Sugamura, K., Nishioka, K., and Nakamura, M. (2006) Prostaglandin D2 plays an essential role in chronic allergic inflammation of the skin via CRTH2 receptor. *J. Immunol*. **177,** 2621–2629.
22. Nagata, K., Hirai, H., Tanaka, K., Ogawa, K., Aso, T., Sugamura, K., Nakamura, M., and Takano, S. (1999) CRTH2, an orphan receptor of T-helper-2-cells, is expressed on basophils and eosinophils and responds to mast cell-derived factor(s). *FEBS Lett*. **459,** 195–199.
23. Yoshimura-Uchiyama, C., Iikura, M., Yamaguchi, M., Nagase, H., Ishii, A., Matsushima, K., Yamamoto, K., Shichijo, M., Bacon, K.B., and Hirai, K. (2004) Differential modulation of human basophil functions through prostaglandin D2 receptors DP and chemoattractant receptor-homologous molecule expressed on Th2 cells/DP2. *Clin. Exp. Allergy* **34,** 1283–1290.
24. Schratl, P., Sturm, E.M., Royer, J.F., Sturm, G.J., Lippe, I.T., Peskar, B.A., and Heinemann, A. (2006) Hierarchy of eosinophil chemoattractants: role of p38 mitogen-activated protein kinase. *Eur. J. Immunol.* **36,** 2401–2409.
25. Powell, W.S. (2003) A novel PGD(2) receptor expressed in eosinophils. *Prostaglandins Leukot. Essent. Fatty Acids* **69,** 179–185.
26. Monneret, G., Li, H., Vasilescu, J., Rokach, J., and Powell, W.S. (2002) 15-Deoxy-delta 12,14-prostaglandins D2 and J2 are potent activators of human eosinophils. *J. Immunol.* **168,** 3563–3569.
27. Jiang, C., Ting, A.T., and Seed, B. (1998) PPAR-gamma agonists inhibit production of monocyte inflammatory cytokines. *Nature* **391,** 82–86.
28. Heinemann, A., Schuligoi, R., Sabroe, I., Hartnell, A., and Peskar, B.A. (2003) Delta 12-prostaglandin J2, a plasma metabolite of prostaglandin D2, causes eosinophil mobilization from the bone marrow and primes eosinophils for chemotaxis. *J. Immunol.* **170,** 4752–4758.
29. Angeli, V., Faveeuw, C., Roye, O., Fontaine, J., Teissier, E., Capron, A., Wolowczuk, I., Capron, M., and Trottein, F. (2001) Role of the parasite-derived prostaglandin D2 in the inhibition of epidermal Langerhans cell migration during schistosomiasis infection. *J. Exp. Med.* **193,** 1135–1147.
30. Faveeuw, C., Gosset, P., Bureau, F., Angeli, V., Hirai, H., Maruyama, T., Narumiya, S., Capron, M., and Trottein, F. (2003) Prostaglandin D2 inhibits the production of interleukin-12 in murine dendritic cells through multiple signaling pathways. *Eur. J. Immunol*. **33**, 889–898.
31. Herve, M., Angeli, V., Pinzar, E., Wintjens, R., Faveeuw, C., Narumiya, S., Capron, A., Urade, Y., Capron, M., Riveau, G., and Trottein, F. (2003) Pivotal roles of the parasite PGD2 synthase and of the host D prostanoid receptor 1 in schistosome immune evasion. *Eur. J. Immunol.* **33,** 2764–2772.
32. Angeli, V., Staumont, D., Charbonnier, A.S., Hammad, H., Gosset, P., Pichavant, M., Lambrecht, B.N., Capron, M., Dombrowicz, D., and Trottein, F. (2004) Activation of the D prostanoid receptor 1 regulates immune and skin allergic responses. *J. Immunol*. **172,** 3822–3829.
33. Hammad, H., de Heer, H.J., Soullie, T., Hoogsteden, H.C., Trottein, F., and Lambrecht, B.N. (2003) Prostaglandin D2 inhibits airway dendritic cell migration and function in steady state conditions by selective activation of the D prostanoid receptor 1. *J. Immunol*. **171,** 3936–3940.
34. Gosset, P., Pichavant, M., Faveeuw, C., Bureau, F., Tonnel, A.B., and Trottein, F. (2005) Prostaglandin D2 affects the differentiation and functions of human dendritic cells: impact on the T cell response. *Eur. J. Immunol*. **35,** 1491–1500.
35. Yokomizo, T., Izumi, T., Chang, K., Takuwa, Y., and Shimizu, T. (1997) A G-protein-coupled receptor for leukotriene B4 that mediates chemotaxis. *Nature* **387,** 620–624.

36. Huang, W.W., Garcia-Zepeda, E.A., Sauty, A., Oettgen, H.C., Rothenberg, M.E., and Luster, A.D. (1998) Molecular and biological characterization of the murine leukotriene B4 receptor expressed on eosinophils. *J. Exp. Med*. **188,** 1063–1074.
37. Tager, A.M. and Luster, A.D. (2003) BLT1 and BLT2: the leukotriene B(4) receptors. *Prostaglandins Leukot. Essent. Fatty Acids* **69,** 123–134.
38. Yokomizo, T., Kato, K., Hagiya, H., Izumi, T., and Shimizu, T. (2001) Hydroxyeicosanoids bind to and activate the low affinity leukotriene B4 receptor, BLT2. *J. Biol. Chem.* **276,** 12454–12459.
39. Pettersson, A., Richter, J., and Owman, C. (2003) Flow cytometric mapping of the leukotriene B4 receptor, BLT1, in human bone marrow and peripheral blood using specific monoclonal antibodies. *Int. Immunopharmacol.* **3,** 1467–1475.
40. Runarsson, G., Liu, A., Mahshid, Y., Feltenmark, S., Pettersson, A., Klein, E., Bjorkholm, M., and Claesson, H.E. (2005) Leukotriene B4 plays a pivotal role in CD40-dependent activation of chronic B lymphocytic leukemia cells. *Blood* **105,** 1274–1279.
41. 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 B4 lipid chemoattractant receptor BLT1 defines antigen-primed T cells in humans. *Blood* **107,** 444–453.
42. Lundeen, K.A., Sun, B., Karlsson, L., and Fourie, A.M. (2006) Leukotriene B4 receptors BLT1 and BLT2: expression and function in human and murine mast cells. *J. Immunol.* **177,** 3439–3447.
43. Gaudreault, E., Thompson, C., Stankova, J., and Rola-Pleszczynski, M. (2005) Involvement of BLT1 endocytosis and Yes kinase activation in leukotriene B4-induced neutrophil degranulation. *J. Immunol.* **174,** 3617–3625.
44. 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 B4. *Proc. Natl. Acad. Sci. U. S. A.* **103,** 6913–6918.
45. Back, M., Bu, D.X., Branstrom, R., Sheikine, Y., Yan, Z.Q., and Hansson, G.K. (2005) Leukotriene B4 signaling through NF-kappaB-dependent BLT1 receptors on vascular smooth muscle cells in atherosclerosis and intimal hyperplasia. *Proc. Natl. Acad. Sci. U. S. A.* **102,** 17501–17506.
46. 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., Luster, A.D., and Gerszten, R.E. (2005) Inhibition of atherogenesis in BLT1-deficient mice reveals a role for LTB4 and BLT1 in smooth muscle cell recruitment. *Circulation* **112,** 578–586.
47. Goldman, D.W. and Goetzl, E.J. (1984) Selective transduction of human polymorphonuclear leukocyte functions by subsets of receptors for leukotriene B4. *J. Allergy Clin. Immunol.* **74,** 373–377.
48. 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.
49. Kamohara, M., Takasaki, J., Matsumoto, M., Saito, T., Ohishi, T., Ishii, H., and Furuichi, K. (2000) Molecular cloning and characterization of another leukotriene B4 receptor. *J. Biol. Chem.* **275,** 27000–27004.
50. Tryselius, Y., Nilsson, N.E., Kotarsky, K., Olde, B., and Owman, C. (2000) Cloning and characterization of cDNA encoding a novel human leukotriene B(4) receptor. *Biochem. Biophys. Res. Commun.* **274,** 377–382.
51. Wang, S., Gustafson, E., Pang, L., Qiao, X., Behan, J., Maguire, M., Bayne, M., and Laz, T. (2000) A novel hepatointestinal leukotriene B4 receptor. Cloning and functional characterization. *J. Biol. Chem*. **275,** 40686–40694.
52. Kato, K., Yokomizo, T., Izumi, T., and Shimizu, T. (2000) Cell-specific transcriptional regulation of human leukotriene B(4) receptor gene. *J. Exp. Med.* **192,** 413–420.
53. Yokomizo, T., Izumi, T., and Shimizu, T. (2001) Co-expression of two LTB4 receptors in human mononuclear cells. *Life Sci*. **68,** 2207–2212.
54. Iizuka, Y., Yokomizo, T., Terawaki, K., Komine, M., Tamaki, K., and Shimizu, T. (2005) Characterization of a mouse second leukotriene B4 receptor, mBLT2: BLT2-dependent ERK activation and cell migration of primary mouse keratinocytes. *J. Biol. Chem.* **280,** 24816–24823.
55. Hoover, H., Karnovasky, M., Austen, K., Corey, E., and Lewis, R. (1984) Leukotriene B4 action on endothelium mediates augmented neutrophil/endothelial adhesion. *Proc. Natl. Acad. Sci. U. S. A.* **81,** 2191–2193.
56. Henderson, W.R., Jr. (1994) The role of leukotrienes in inflammation. *Ann. Intern. Med.* **121,** 684–697.
57. Pettersson, A., Boketoft, A., Sabirsh, A., Nilsson, N.E., Kotarsky, K., Olde, B., and Owman, C. (2000) First-generation monoclonal antibodies identifying the human leukotriene B(4) receptor-1. *Biochem. Biophys. Res. Commun.* **279,** 520–525.
58. Iikura, M., Suzukawa, M., Yamaguchi, M., Sekiya, T., Komiya, A., Yoshimura-Uchiyama, C., Nagase, H., Matsushima, K., Yamamoto, K., and Hirai, K. (2005) 5-Lipoxygenase products regulate basophil functions: 5-Oxo-ETE elicits migration, and leukotriene B(4) induces degranulation. *J. Allergy Clin. Immunol*. **116,** 578–585.
59. Chiang, N., Gronert, K., Clish, C.B., O'Brien, J.A., Freeman, M.W., and Serhan, C.N. (1999) Leukotriene B4 receptor transgenic mice reveal novel protective roles for lipoxins and aspirin-triggered lipoxins in reperfusion. *J. Clin. Invest.* **104,** 309–316.
60. Showell, H.J., Pettipher, E.R., Cheng, J.B., Breslow, R., Conklyn, M.J., Farrell, C.A., Hingorani, G.P., Salter, E.D., Hackman, B.C., Wimberly, D.J., et al. (1995) The in vitro and in vivo pharmacologic activity of the potent and selective leukotriene B4 receptor antagonist CP-105696. *J. Pharmacol. Exp. Ther*. **273**, 176–184.
61. Murray, J., Ward, C., O'Flaherty, J.T., Dransfield, I., Haslett, C., Chilvers, E.R., and Rossi, A.G. (2003) Role of

leukotrienes in the regulation of human granulocyte behaviour: dissociation between agonist-induced activation and retardation of apoptosis. *Br. J. Pharmacol.* **139,** 388–398.

62. Stankova, J., Turcotte, S., Harris, J., and Rola-Pleszczynski, M. (2002) Modulation of leukotriene B4 receptor-1 expression by dexamethasone: potential mechanism for enhanced neutrophil survival. *J. Immunol.* **168,** 3570–3576.
63. Gaudreault, E., Stankova, J., and Rola-Pleszczynski, M. (2005) Involvement of leukotriene B4 receptor 1 signaling in platelet-activating factor-mediated neutrophil degranulation and chemotaxis. *Prostaglandins Other Lipid Mediat.* **75,** 25–34.
64. Showell, H.J., Breslow, R., Conklyn, M.J., Hingorani, G.P., and Koch, K. (1996) Characterization of the pharmacological profile of the potent LTB4 antagonist CP-105,696 on murine LTB4 receptors in vitro. *Br. J. Pharmacol.* **117**, 1127–1132.
65. Young, R.E., Thompson, R.D., and Nourshargh, S. (2002) Divergent mechanisms of action of the inflammatory cytokines interleukin 1-beta and tumour necrosis factor-alpha in mouse cremasteric venules. *Br. J. Pharmacol.* **137,** 1237–1246.
66. Griffiths, R.J., Pettipher, E.R., Koch, K., Farrell, C.A., Breslow, R., Conklyn, M.J., Smith, M.A., Hackman, B.C., Wimberly, D.J., Milici, A.J., et al. (1995) Leukotriene B4 plays a critical role in the progression of collagen-induced arthritis. *Proc. Natl. Acad. Sci. U. S. A.* **92,** 517–521.
67. Kim, N.D., Chou, R.C., Seung, E., Tager, A.M., and Luster, A.D. (2006) A unique requirement for the leukotriene B4 receptor BLT1 for neutrophil recruitment in inflammatory arthritis. *J. Exp. Med.* **203,** 829–835.
68. Rios-Santos, F., Benjamim, C.F., Zavery, D., Ferreira, S.H., and Cunha Fde, Q. (2003) A critical role of leukotriene B4 in neutrophil migration to infectious focus in cecal ligaton and puncture sepsis. *Shock* **19,** 61–65.
69. Noiri, E., Yokomizo, T., Nakao, A., Izumi, T., Fujita, T., Kimura, S., and Shimizu, T. (2000) An in vivo approach showing the chemotactic activity of leukotriene B(4) in acute renal ischemic-reperfusion injury. *Proc. Natl. Acad. Sci. U. S. A.* **97,** 823–828.
70. Tager, A.M., Dufour, J.H., Goodarzi, K., Bercury, S.D., von Andrian, U.H., and Luster, A.D. (2000) BLTR mediates leukotriene B(4)-induced chemotaxis and adhesion and plays a dominant role in eosinophil accumulation in a murine model of peritonitis. *J. Exp. Med.* **192,** 439–446.
71. Haribabu, B., Verghese, M.W., Steeber, D.A., Sellars, D.D., Bock, C.B., and Snyderman, R. (2000) Targeted disruption of the leukotriene B(4) receptor in mice reveals its role in inflammation and platelet-activating factor-induced anaphylaxis. *J. Exp. Med*. **192,** 433–438.
72. Terawaki, K., Yokomizo, T., Nagase, T., Toda, A., Taniguchi, M., Hashizume, K., Yagi, T., and Shimizu, T. (2005) Absence of leukotriene B4 receptor 1 confers resistance to airway hyperresponsiveness and Th2-type immune responses. *J. Immunol*. **175,** 4217–4225.
73. Medoff, B.D., Tager, A.M., Jackobek, R., Means, T.K., Wang, L., and Luster, A.D. (2006) Antibody-antigen interaction in the airway drives early granulocyte recruitment through BLT1. *Am. J. Physiol. Lung Cell. Mol. Physiol*. **290,** L170–178.
74. Chen, M., Lam, B.K., Kanaoka, Y., Nigrovic, P.A., Audoly, L.P., Austen, K.F., and Lee, D.M. (2006) Neutrophil-derived leukotriene B4 is required for inflammatory arthritis. *J. Exp. Med.* **203,** 837–842.
75. Teixeira, M.M., Giembycz, M.A., Lindsay, M.A., and Hellewell, P.G. (1997) Pertussis toxin shows distinct early signalling events in platelet-activating factor-, leukotriene B4-, and C5a-induced eosinophil homotypic aggregation in vitro and recruitment in vivo. *Blood* **89**, 4566–4573.
76. Takafuji, S., Tadokoro, K., Ito, K., and Nakagawa, T. (1998) Release of granule proteins from human eosinophils stimulated with mast-cell mediators. *Allergy* **53,** 951–956.
77. Lindsay, M.A., Perkins, R.S., Barnes, P.J., and Giembycz, M.A. (1998) Leukotriene B4 activates the NADPH oxidase in eosinophils by a pertussis toxin-sensitive mechanism that is largely independent of arachidonic acid mobilization. *J. Immunol*. **160,** 4526–4534.
78. Gladue, R.P., Carroll, L.A., Milici, A.J., Scampoli, D.N., Stukenbrok, H.A., Pettipher, E.R., Salter, E.D., Contillo, L., and Showell, H.J. (1996) Inhibition of leukotriene B4-receptor interaction suppresses eosinophil infiltration and disease pathology in a murine model of experimental allergic encephalomyelitis. *J. Exp. Med*. **183,** 1893–1898.
79. Klein, A., Talvani, A., Cara, D.C., Gomes, K.L., Lukacs, N.W., and Teixeira, M.M. (2000) Stem cell factor plays a major role in the recruitment of eosinophils in allergic pleurisy in mice via the production of leukotriene B4. *J. Immunol.* **164,** 4271–4276.
80. Klein, A., Talvani, A., Silva, P.M., Martins, M.A., Wells, T.N., Proudfoot, A., Luckacs, N.W., and Teixeira, M.M. (2001) Stem cell factor-induced leukotriene B4 production cooperates with eotaxin to mediate the recruitment of eosinophils during allergic pleurisy in mice. *J. Immunol*. **167,** 524–531.
81. Weller, C.L., Collington, S.J., Brown, J.K., Miller, H.R., Al-Kashi, A., Clark, P., Jose, P.J., Hartnell, A., and Williams, T.J. (2005) Leukotriene B4, an activation product of mast cells, is a chemoattractant for their progenitors. *J. Exp. Med*. **201,** 1961–1971.
82. Pettersson, A., Sabirsh, A., Bristulf, J., Kidd-Ljunggren, K., Ljungberg, B., Owman, C., and Karlsson, U. (2005) Pro- and anti-inflammatory substances modulate expression of the leukotriene B4 receptor, BLT1, in human monocytes. *J. Leukoc. Biol*. **77**, 1018–1025.
83. 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 B4 strongly increases monocyte chemoattractant protein-1 in human monocytes.

Arterioscler. Thromb. Vasc. Biol. **24**, 1783–1788.

84. 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 B4. *J. Immunol.* **163,** 6148–6154.
85. Aiello, R.J., Bourassa, P.A., Lindsey, S., Weng, W., Freeman, A., and Showell, H.J. (2002) Leukotriene B4 receptor antagonism reduces monocytic foam cells in mice. *Arterioscler. Thromb. Vasc. Biol.* **22,** 443–449.
86. 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.
87. Payan, D.G. and Goetzl, E.J. (1984) Recognition of leukotriene B4 by a unique subset of human T-lymphocytes. *J. Allergy Clin. Immunol*. **74,** 403–406.
88. Leppert, D., Hauser, S.L., Kishiyama, J.L., An, S., Zeng, L., and Goetzl, E.J. (1995) Stimulation of matrix metalloproteinase-dependent migration of T cells by eicosanoids. *FASEB J.* **9,** 1473–1481.
89. 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 B4 receptor BLT1 mediates early effector T cell recruitment. *Nat. Immunol.* **4**, 982–990.
90. Goodarzi, K., Goodarzi, M., Tager, A.M., Luster, A.D., and von Andrian, U.H. (2003) Leukotriene B4 and BLT1 control cytotoxic effector T cell recruitment to inflamed tissues. *Nat. Immunol.* **4,** 965–973.
91. 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 B4. *Nat. Immunol.* **4,** 974–981.
92. Taube, C., Miyahara, N., Ott, V., Swanson, B., Takeda, K., Loader, J., Shultz, L.D., Tager, A.M., Luster, A.D., Dakhama, A., and Gelfand, E.W. (2006) The leukotriene B4 receptor (BLT1) is required for effector CD8+ T cell-mediated, mast cell-dependent airway hyperresponsiveness. *J. Immunol.* **176**, 3157–3164.
93. Miyahara, N., Takeda, K., Miyahara, S., Taube, C., Joetham, A., Koya, T., Matsubara, S., Dakhama, A., Tager, A.M., Luster, A.D., and Gelfand, E.W. (2005) Leukotriene B4 receptor-1 is essential for allergen-mediated recruitment of CD8+ T cells and airway hyperresponsiveness. *J. Immunol.* **174,** 4979–4984.
94. Weringer, E.J., Perry, B.D., Sawyer, P.S., Gilman, S.C., and Showell, H.J. (1999) Antagonizing leukotriene B4 receptors delays cardiac allograft rejection in mice. *Transplantation* **67,** 808–815.
95. Medoff, B.D., Seung, E., Wain, J.C., Means, T.K., Campanella, G.S., Islam, S.A., Thomas, S.Y., Ginns, L.C., Grabie, N., Lichtman, A.H., Tager, A.M., and Luster, A.D. (2005) BLT1-mediated T cell trafficking is critical for rejection and obliterative bronchiolitis after lung transplantation. *J. Exp. Med*. **202,** 97–110.
96. Liao, T., Ke, Y., Shao, W.H., Haribabu, B., Kaplan, H.J., Sun, D., and Shao, H. (2006) Blockade of the interaction of leukotriene b4 with its receptor prevents development of autoimmune uveitis. *Invest. Ophthalmol. Vis. Sci*. **47,** 1543–1549.
97. 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 B4 receptors: a role for LTB4 in up-regulation of CCR7 expression and function. *Blood* **109(2),** 626–631.
98. Shin, E.H., Lee, H.Y., and Bae, Y.S. (2006) Leukotriene B4 stimulates human monocyte-derived dendritic cell chemotaxis. *Biochem. Biophys. Res. Commun.* **348**, 606–611.
99. Busse, W. and Kraft, M. (2005) Cysteinyl leukotrienes in allergic inflammation: strategic target for therapy. *Chest* **127,** 1312–1326.
100. Lynch, K.R., O'Neill, 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., Austin, C.P., Chateauneuf, A., Stocco, R., Greig, G.M., Kargman, S., Hooks, S.B., Hosfield, E., Williams, D.L., Jr., Ford-Hutchinson, A.W., Caskey, C.T., and Evans, J.F. (1999) Characterization of the human cysteinyl leukotriene CysLT1 receptor. *Nature* **399,** 789–793.
101. Sarau, H.M., Ames, R.S., Chambers, J., Ellis, C., Elshourbagy, N., Foley, J.J., Schmidt, D.B., Muccitelli, R.M., Jenkins, O., Murdock, P.R., Herrity, N.C., Halsey, W., Sathe, G., Muir, A.I., Nuthulaganti, P., Dytko, G.M., Buckley, P.T., Wilson, S., Bergsma, D.J., and Hay, D.W. (1999) Identification, molecular cloning, expression, and characterization of a cysteinyl leukotriene receptor. *Mol. Pharmacol*. **56**, 657–663.
102. Hoshino, M., Izumi, T., and Shimizu, T. (1998) Leukotriene D4 activates mitogen-activated protein kinase through a protein kinase Calpha-Raf-1-dependent pathway in human monocytic leukemia THP-1 cells. *J. Biol. Chem*. **273,** 4878–4882.
103. Figueroa, D.J., Breyer, R.M., Defoe, S.K., Kargman, S., Daugherty, B.L., Waldburger, K., Liu, Q., Clements, M., Zeng, Z., O'Neill, G.P., Jones, T.R., Lynch, K.R., Austin, C.P., and Evans, J.F. (2001) Expression of the cysteinyl leukotriene 1 receptor in normal human lung and peripheral blood leukocytes. *Am. J. Respir. Crit. Care Med.* **163**, 226–233.
104. 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.
105. Bautz, F., Denzlinger, C., Kanz, L., and Mohle, R. (2001) Chemotaxis and transendothelial migration of CD34(+) hematopoietic progenitor cells induced by the inflammatory mediator leukotriene D4 are mediated by the 7-transmembrane receptor CysLT1. *Blood* **97,** 3433–3440.

106. Yang, G., Haczku, A., Chen, H., Martin, V., Galczenski, H., Tomer, Y., Van Besien, C.R., Evans, J.F., Panettieri, R.A., and Funk, C.D. (2004) Transgenic smooth muscle expression of the human CysLT1 receptor induces enhanced responsiveness of murine airways to leukotriene D4. *Am. J. Physiol. Lung Cell. Mol. Physiol*. **286,** L992–1001.
107. Maekawa, A., Kanaoka, Y., Lam, B.K., and Austen, K.F. (2001) Identification in mice of two isoforms of the cysteinyl leukotriene 1 receptor that result from alternative splicing. *Proc. Natl. Acad. Sci. U. S. A.* **98,** 2256–2261.
108. Martin, V., Sawyer, N., Stocco, R., Unett, D., Lerner, M.R., Abramovitz, M., and Funk, C.D. (2001) Molecular cloning and functional characterization of murine cysteinyl-leukotriene 1 (CysLT(1)) receptors. *Biochem. Pharmacol*. **62**, 1193–1200.
109. Ogasawara, H., Ishii, S., Yokomizo, T., Kakinuma, T., Komine, M., Tamaki, K., Shimizu, T., and Izumi, T. (2002) Characterization of mouse cysteinyl leukotriene receptors mCysLT1 and mCysLT2: differential pharmacological properties and tissue distribution. *J. Biol. Chem.* **277,** 18763–18768.
110. Peters-Golden, M., Gleason, M.M., and Togias, A. (2006) Cysteinyl leukotrienes: multi-functional mediators in allergic rhinitis. *Clin. Exp. Allergy* **36**, 689–703.
111. Heise, C.E., O'Dowd, B.F., Figueroa, D.J., Sawyer, N., Nguyen, T., Im, D.S., Stocco, R., Bellefeuille, J.N., Abramovitz, M., Cheng, R., Williams, D.L., Jr., Zeng, Z., Liu, Q., Ma, L., Clements, M.K., Coulombe, N., Liu, Y., Austin, C.P., George, S.R., O'Neill, G.P., Metters, K.M., Lynch, K.R., and Evans, J.F. (2000) Characterization of the human cysteinyl leukotriene 2 receptor. *J. Biol. Chem*. **275**, 30531–30536.
112. Nothacker, H.P., Wang, Z., Zhu, Y., Reinscheid, R.K., Lin, S.H., and Civelli, O. (2000) Molecular cloning and characterization of a second human cysteinyl leukotriene receptor: discovery of a subtype selective agonist. *Mol. Pharmacol*. **58,** 1601–1608.
113. Takasaki, J., Kamohara, M., Matsumoto, M., Saito, T., Sugimoto, T., Ohishi, T., Ishii, H., Ota, T., Nishikawa, T., Kawai, Y., Masuho, Y., Isogai, T., Suzuki, Y., Sugano, S., and Furuichi, K. (2000) The molecular characterization and tissue distribution of the human cysteinyl leukotriene CysLT(2) receptor. *Biochem. Biophys. Res. Commun*. **274,** 316–322.
114. Lotzer, K., Spanbroek, R., Hildner, M., Urbach, A., Heller, R., Bretschneider, E., Galczenski, H., Evans, J.F., and Habenicht, A.J. (2003) Differential leukotriene receptor expression and calcium responses in endothelial cells and macrophages indicate 5-lipoxygenase-dependent circuits of inflammation and atherogenesis. *Arterioscler. Thromb. Vasc. Biol*. **23**, e32–36.
115. 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. U. S. A.* **100,** 11589–11593.
116. Hui, Y., Yang, G., Galczenski, H., Figueroa, D.J., Austin, C.P., Copeland, N.G., Gilbert, D.J., Jenkins, N.A., and Funk, C.D. (2001) The murine cysteinyl leukotriene 2 (CysLT2) receptor. cDNA and genomic cloning, alternative splicing, and in vitro characterization. *J. Biol. Chem.* **276,** 47489–47495.
117. Kim, D.C., Hsu, F.I., Barrett, N.A., Friend, D.S., Grenningloh, R., Ho, I.C., Al-Garawi, A., Lora, J.M., Lam, B.K., Austen, K.F., and Kanaoka, Y. (2006) Cysteinyl leukotrienes regulate Th2 cell-dependent pulmonary inflammation. *J. Immunol*. **176,** 4440–4448.
118. Henderson, W.R., Jr., Tang, L.O., Chu, S.J., Tsao, S.M., Chiang, G.K., Jones, F., Jonas, M., Pae, C., Wang, H., and Chi, E.Y. (2002) A role for cysteinyl leukotrienes in airway remodeling in a mouse asthma model. *Am. J. Respir. Crit. Care Med.* **165**, 108–116.
119. Fregonese, L., Silvestri, M., Sabatini, F., and Rossi, G.A. (2002) Cysteinyl leukotrienes induce human eosinophil locomotion and adhesion molecule expression via a CysLT1 receptor-mediated mechanism. *Clin. Exp. Allergy* **32,** 745–750.
120. Nagata, M., Saito, K., Tsuchiya, K., and Sakamoto, Y. (2002) Leukotriene D4 upregulates eosinophil adhesion via the cysteinyl leukotriene 1 receptor. *J. Allergy Clin. Immunol.* **109,** 676–680.
121. Virchow, J.C., Jr., Faehndrich, S., Nassenstein, C., Bock, S., Matthys, H., and Luttmann, W. (2001) Effect of a specific cysteinyl leukotriene-receptor 1-antagonist (montelukast) on the transmigration of eosinophils across human umbilical vein endothelial cells. *Clin. Exp. Allergy* **31,** 836–844.
122. Saito, H., Morikawa, H., Howie, K., Crawford, L., Baatjes, A.J., Denburg, E., Cyr, M.M., and Denburg, J.A. (2004) Effects of a cysteinyl leukotriene receptor antagonist on eosinophil recruitment in experimental allergic rhinitis. *Immunology* **113,** 246–252.
123. 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.
124. 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.
125. 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.
126. 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.
127. Thivierge, M., Stankova, J., and Rola-Pleszczynski, M. (2001) IL-13 and IL-4 up-regulate cysteinyl leukotriene 1 receptor expression in human monocytes and macrophages. *J. Immunol.* **167,** 2855–2860.
128. Woszczek, G., Pawliczak, R., Qi, H.Y., Nagineni, S., Alsaaty, S., Logun, C., and Shelhamer, J.H. (2005) Functional

characterization of human cysteinyl leukotriene 1 receptor gene structure. *J. Immunol*. **175,** 5152–5159.

129. Hung, C.H., Li, C.Y., Hua, Y.M., Chen, C.J., Yang, K.D., and Jong, Y.J. (2006) Effects of leukotriene receptor antagonists on monocyte chemotaxis, p38 and cytoplasmic calcium. *Pediatr. Allergy Immunol.* **17,** 250–258.
130. Mellor, E.A., Maekawa, A., Austen, K.F., and Boyce, J.A. (2001) Cysteinyl leukotriene receptor 1 is also a pyrimidinergic receptor and is expressed by human mast cells. *Proc. Natl. Acad. Sci. U. S. A.* **98,** 7964–7969.
131. Sjostrom, M., Jakobsson, P.J., Juremalm, M., Ahmed, A., Nilsson, G., Macchia, L., and Haeggstrom, J.Z. (2002) Human mast cells express two leukotriene C(4) synthase isoenzymes and the CysLT(1) receptor. *Biochim. Biophys. Acta* **1583,** 53–62.
132. Jiang, Y., Kanaoka, Y., Feng, C., Nocka, K., Rao, S., and Boyce, J.A. (2006) Cutting edge: interleukin 4-dependent mast cell proliferation requires autocrine/intracrine cysteinyl leukotriene-induced signaling. *J. Immunol.* **177,** 2755–2759.
133. Robbiani, D.F., Finch, R.A., Jager, D., Muller, W.A., Sartorelli, A.C., and Randolph, G.J. (2000) The leukotriene C(4) transporter MRP1 regulates CCL19 (MIP-3beta, ELC)-dependent mobilization of dendritic cells to lymph nodes. *Cell* **103,** 757–768.
134. 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.
135. Parameswaran, K., Liang, H., Fanat, A., Watson, R., Snider, D.P., and O'Byrne, P.M. (2004) Role for cysteinyl leukotrienes in allergen-induced change in circulating dendritic cell number in asthma. *J. Allergy Clin. Immunol*. **114,** 73–79.
136. Saeki, S., Matsuse, H., Kondo, Y., Machida, I., Kawano, T., Tomari, S., Obase, Y., Fukushima, C., and Kohno, S. (2004) Effects of antiasthmatic agents on the functions of peripheral blood monocyte-derived dendritic cells from atopic patients. *J. Allergy Clin. Immunol.* **114,** 538–544.
137. Thompson, C., Cloutier, A., Bosse, Y., Thivierge, M., Gouill, C.L., Larivee, P., McDonald, P.P., Stankova, J., and Rola-Pleszczynski, M. (2006) CysLT1 receptor engagement induces activator protein-1- and NF-kappaB-dependent IL-8 expression. *Am. J. Respir. Cell Mol. Biol.* **35,** 697–704.
138. 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.
139. Okunishi, K., Dohi, M., Nakagome, K., Tanaka, R., and Yamamoto, K. (2004) A novel role of cysteinyl leukotrienes to promote dendritic cell activation in the antigen-induced immune responses in the lung. *J. Immunol.* **173,** 6393–6402.
140. 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 alpha beta- and gamma delta effector T cells. *J. Immunol.* **175,** 713–719.
141. Spinozzi, F., Russano, A.M., Piattoni, S., Agea, E., Bistoni, O., de Benedictis, D., and de Benedictis, F.M. (2004) Biological effects of montelukast, a cysteinyl-leukotriene receptor-antagonist, on T lymphocytes. *Clin. Exp. Allergy* **34,** 1876–1882.
142. Honig, S.M., Fu, S., Mao, X., Yopp, A., Gunn, M.D., Randolph, G.J., and Bromberg, J.S. (2003) FTY720 stimulates multidrug transporter- and cysteinyl leukotriene-dependent T cell chemotaxis to lymph nodes. *J. Clin. Invest.* **111,** 627–637.
143. Lamoureux, J., Stankova, J., and Rola-Pleszczynski, M. (2006) Leukotriene D4 enhances immunoglobulin production in CD40-activated human B lymphocytes. *J. Allergy Clin. Immunol.* **117,** 924–930.

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