

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 D₂, DP₁ and DP₂/CRTH2; the receptors for leukotriene B₄, BLT₁ and BLT₂; and the receptors for the cysteinyl leukotrienes, CysLT₁ and CysLT₂, 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 D₂, DP₁, DP₂, CRTH2, leukotriene B₄, BLT₁, BLT₂, cysteinyl leukotriene, CysLT₁, CysLT₂

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 A₂ (PLA₂), 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 D₂, leukotriene B₄, and the cysteinyl leukotrienes LTC₄, LTD₄, and LTE₄ 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.

THE PROSTAGLANDIN RECEPTORS DP₁ AND DP₂/CRTH2

Prostaglandin D₂ (PGD₂) 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 PGD₂ within bronchoalveolar lavage fluids[2] and in allergic skin biopsies[3] of antigen-challenged patients. DP₁, the first identified receptor for PGD₂, is a prostanoid G-protein coupled-type receptor with 73% homology at the amino acid level between the human and mouse forms[4]. DP₁ preferentially binds the ligand PGD₂ with a K_d of 1.5 nM, in addition to the selective DP₁ agonist BW245C and DP₁ antagonist BWA868C with equal affinities, and binds with 100-fold or less affinity to PGE₂, PGF_{2α}, iloprost, and the thromboxane A₂ mimetic U46619. Binding of DP₁ by PGD₂ results in the elevation of intracellular cyclic AMP (cAMP) levels and Ca²⁺ mobilization, but not the production of inositol 1,4,5-triphosphate (IP₃)[5]. In organ tissues, DP₁ is expressed at low levels in the small intestine and retina in humans[5], while in mice, DP₁ is found in the ileum, lung, stomach, and uterus[6]. In the original description of human DP₁, basophils were the only human leukocytes found to express DP₁, but since then, DP₁ 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 DP₁. In an ovalbumin (OVA)-induced murine model of asthma, mice deficient in the DP₁ receptor demonstrated decreased levels of eosinophils and lymphocytes, and the cytokines IL-4, IL-5, and IL-13, suggesting that DP₁ plays a critical role in the induction of Th2-mediated allergic responses[11] (Table 1).

TABLE 1
DP₁ and DP₂/CRTH2 Receptors

	DP ₁	DP ₂ /CRTH2
Receptor expression on leukocytes	<i>Human:</i> eosinophils, basophils, monocytes, dendritic cells, Th1 and Th2 cells <i>Mouse:</i> monocytes, dendritic cells, eosinophils	<i>Human:</i> Th2 cells, type 2 cytotoxic cells, basophils, eosinophils, monocytes <i>Mouse:</i> Th1 and Th2 cells, eosinophils, monocytes, mast cell
Agonists	PGD ₂ = PDJ ₂ BW245C ZK110841 SQ27986	PGD ₂ = PGJ ₂ = 15d-PGD ₂ = DK-PGD ₂ >Δ ¹² -PGJ ₂ indomethacin
Antagonists	BWA868C AH6809	BM7 (neutralizing antibody) Ramatroban (BAY-u3405)

However, certain data suggested that PGD₂ might activate leukocytes through an alternate receptor to DP₁. In the OVA-induced asthma model, DP₁ up-regulation in the lung primarily occurs on the airway epithelium, and serum IgE levels and Th2 cytokine production by antigen-stimulated splenocytes from DP₁-deficient mice is preserved, indicating intact immune responses[11]. Activation of DP₁ through G_{sα} proteins results in an increase of intracellular cAMP typically associated with dampening of cellular effector function, contrary to the immune cell activation observed in PGD₂-high states, such as asthma and allergic responses. In addition, PGD₂ induces eosinophil chemotaxis, CD11b expression, and L-selectin expression in a manner neither replicated by the DP₁ receptor agonist BW245C nor inhibited by DP₁ receptor antagonist BWA868C[12], leading investigators to postulate that there existed a separate PGD₂ receptor whose proinflammatory functions were diametrically opposed to the suppressive effects of DP₁ 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 PGD₂

as the mast cell–derived ligand for CRTH2, which is now also known as DP₂. Unlike DP₁ and the other prostanoid receptors, DP₂ 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 BLT₁ and CysLT₁[14]. Activation of DP₂ leads to depression of intracellular cAMP levels, Ca²⁺ mobilization, and generation of diacylglycerol (DAG) and IP₃ through G_i protein signaling[15]. DP₂ 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, DP₂ mRNA is found at low levels in the lung, liver, kidney, brain, heart, thymus, and spleen[17]. In human peripheral blood leukocytes, DP₂ 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 DP₂ 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).

DP₁ and DP₂ and T Cells

The DP₂ 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 DP₂ -positive, with the majority of the DP₂ -positive CD4⁺ T cells being activated effector/memory T cells as indicated by CD45RA⁻, CD45RO⁺, and CD25⁺ staining[13]. Subsequent studies confirmed that DP₂ 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, DP₂ activation by PGD₂ and the DP₂-specific agonist 13,14-dihydro-15-keto PGD₂ (DK-PGD₂) induces chemotaxis[14] and CD11b up-regulation[9] in Th2 cells, while the DP₁ agonist BW245C does not. PGD₂ induces Th2 cell production of IL-4, IL-5, and IL-13, a result that is replicated to a lesser extent by the DK-PGD₂, but not BW245C, indicating activity through DP₂[9,19]. These results demonstrate that DP₂ 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 DP₁ expression in human T cells[14], addition of PGD₂ or the DP₁ 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 DP₂ agonist DK-PGD₂ has no effect on the production of these cytokines, indicating this PGD₂ effect is mediated through selective DP₁ activation[9]. In addition, selective DP₁ 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), DP₁ mRNA becomes detectable in both Th1 and Th2 cells at low levels[9]. However, competitive binding assays show that DP₂ is the dominant receptor on Th2 cells by preferentially binding PGD₂ over DP₁[19]. Therefore, these studies demonstrate that DP₁ may provide a counter-regulatory effect on Th2 cells in opposition to DP₂, suggesting that DP₂ antagonists may actually further suppress Th2 responses not only by blocking DP₂, but also by increasing the availability of PGD₂ to bind DP₁ that would otherwise activate DP₂.

Although mouse DP₂ shares significant homology with the human DP₂ receptor, a significant distinction between the two species is the fact that DP₂ is expressed on both Th1 and Th2 subsets in mice[17], suggesting that a strict dichotomy between DP₂ regulation of Th1 and Th2 subsets may not exist in this species. Surprisingly, DP₂^{-/-} 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 DP₂^{-/-} mice generates significantly more IL-5 than wild-type T cells[20], suggesting that DP₂ may actually play an anti-inflammatory role in mice by suppressing T-cell production of Th2 cytokines in mice. DP₂^{-/-} 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 DP₂^{-/-} 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 DP₂ selective agonist DK-PGD₂ exacerbates mouse models of asthma and atopic dermatitis[10], which instead suggest a proinflammatory role for murine DP₂.

These collective studies clearly indicate a dominant role for DP₂ in the direct activation of Th2 cells in humans. Although data suggest that DP₁ activation of T cells may play a counter-regulatory role by suppressing cytokine production and inhibiting leukocyte movement, the precise physiological relevance of DP₁ receptor activation on human Th1 and Th2 cells still remains to be defined more fully, requiring further dedicated studies of DP₁ activation on separate Th1 and Th2 cellular populations. In mice, the role of DP₂ activation on T cells and its role in disease pathogenesis is less well delineated, with the coincident existence of DP₂ on both Th1 and Th2 populations and conflicting phenotypes in allergic disease models, indicating that DP₂ may not play as critical a role in inducing Th2 responses in mice as in humans.

DP₁ and DP₂ in Eosinophils and Basophils

PGD₂ is a major eicosanoid product of mast cells, and levels of PGD₂ are elevated in allergic responses, suggesting an important role for PGD₂ in eosinophil activation. Addition of PGD₂ to eosinophils induces a number of proinflammatory responses, including chemokinesis, degranulation, and leukotriene production. Both PGD₂ receptors, DP₁ and DP₂, are expressed on human basophils[14] and eosinophils[7,22]. Through the use of DP₁- and DP₂-specific agonists, DP₂ has been identified as the critical receptor for eosinophil chemokinesis, chemotaxis, CD11b up-regulation, and degranulation, while selective DP₁ activation inhibits eosinophil apoptosis in culture conditions[7,12]. PGD₂ also induces similar responses in basophils through DP₂ activation, although DP₁ stimulation does not have antiapoptotic effects in this population[23]. Pretreatment of eosinophils with PGD₂ enhances their chemotaxis towards eotaxin-1 and 5-oxo-6,8,11,14-eicosatetraenoic acid (5-oxo-ETE) through activation of the DP₂ receptor, while PGD₂ activation of DP₂ suppresses basophil chemotaxis to these agents, indicating that DP₂ activation may preferentially augment eosinophil migration towards other subsequently encountered chemoattractants[24]. Therefore, although DP₁ and DP₂ are coexpressed on eosinophils and bind to PGD₂ with roughly equal affinities[14], DP₂ appears to exert a dominant proinflammatory effect on these cells. This effect may be explained, in part, by the relatively low expression of DP₁ on eosinophils compared with DP₂, which may up-regulated under inflammatory conditions[15].

PGD₂ 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 DP₁ and DP₂ activation. PGJ₂ is the initial dehydration product of PGD₂, which can then be further metabolized to 15-dexoxy- $\Delta^{12,14}$ -PGJ₂ (15d-PGJ₂) and Δ^{12} -PGJ₂, all of which are found in blood plasma incubated with PGD₂[25]. While PGJ₂ binds to both DP₁ and DP₂, 15d-PGD₂ selectively binds DP₂ over DP₁[14]. At low concentrations (10^6 – 10^9 M), 15d-PGJ₂ induces eosinophil calcium flux, actin polymerization, and CD11b expression, while it has no effect on DP₁-mediated platelet aggregation[26]. These results contrast previous findings that 15d-PGJ₂ (at micromolar concentrations) possesses anti-inflammatory effects by inhibiting monocyte cytokine production and release through activation of peroxisome proliferator-activated receptor- γ (PPAR γ)[27]. Δ^{12} -PGJ₂ 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} -PGJ₂ binds with weak affinity to both DP₁ and DP₂[14], DP₁ activation does not lead to significant calcium flux or chemotaxis in eosinophils, leading the authors to hypothesize that these proinflammatory Δ^{12} -PGJ₂-mediated effects on eosinophils occur through DP₂ stimulation rather than DP₁.

In mice as in humans, both DP₁ and DP₂ are expressed on eosinophils. In *in vitro* chemotaxis studies, PGD₂ induces migration of eosinophils by activation of DP₂, while DP₁ activation has no such effect.

Addition of the DP₂ agonist DK-PGD₂ increases organ eosinophilia in models of OVA-induced asthma and atopic dermatitis in mice[10], suggesting that DP₂ 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 PGD₂ receptors has paradoxically yielded opposite results. DP₁^{-/-} mice have decreased airway eosinophilia in an OVA-induced asthma model[11], while DP₂^{-/-} 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 DP₂^{-/-} 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 PGD₂ in inducing eosinophilic inflammation in mice occurs by mechanisms more complex than directly inducing eosinophil activation and movement. Although *in vitro* studies show that DP₂ is capable of directly activating eosinophils, *in vivo* PGD₂-mediated allergic effects may depend on cooperation of resident cells that are organ -or site-specific. In murine lungs, DP₁ 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 DP₁-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, PGD₂ may play a predominant role by activating DP₁ receptors on epithelium and generating eosinophil chemoattractants other than PGD₂, which would be consistent with the findings that DP₂^{-/-} mice do not exhibit reduced inflammation.

DP₁ and DP₂ in Dendritic Cells

DP₁ and DP₂ are both expressed on murine dendritic cells[29,30]. A role for PGD₂-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 PGD₂ production in the skin and retention of LCs within the skin through DP₁ receptor activation[29]. Further studies showed that *S. mansoni* produces PGD₂ through the parasitic enzyme Sm28GST, which shares 32% homology with hematopoietic-type PGD synthase[31], implying that parasite generation of PGD₂ and subsequent inhibition of dendritic cell migration through DP₁ activation evolved as a means for parasites to evade the immune system. Indeed, DP₁-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 DP₁ signaling[31].

Subsequently, similar roles for DP₁ regulation of dendritic cells have been found in other inflammation models. In a mouse contact hypersensitivity model, pretreatment with the DP₁ 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, DP₁ 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 DP₁ 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, DP₁, but not DP₂, 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 DP₁ and DP₂ are found in human dendritic cells, flow cytometry analysis demonstrates significant expression of only DP₁ on both immature and mature DCs[8]. Both TNF-induced migration of LCs *in vitro* and chemotaxis to CCL20/MIP-3 α and CCL19/ELC are inhibited by

DP₁ activation, without altering expression levels of their receptors CCR6 and CCR7[32]. Similarly, PGD₂ and the DP₁ agonist BW245C inhibit CCL5/RANTES- and CCL19/ELC-induced chemotaxis of monocyte-derived DCs (MoDCs). Unlike LCs, incubation of MoDCs in the presence of PGD₂ alters their expression of cell surface markers and costimulatory molecules, notably decreasing CCR7 and subsequent ability to migrate towards CCL19/ELC[8,34]. PGD₂ 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 PGD₂ 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 DP₁ agonism with BW245C and not reproduced with DP₂ agonist, but some functions such as alteration of cell surface markers appear to be induced by PGD₂ alone, implying that PGD₂ may also affect DCs in a DP₁-independent manner. Collectively, these data indicate a role for PGD₂/DP₁ in suppressing the migration of DCs out of tissues to the draining lymph nodes and in favoring Th2 responses.

THE LTB₄ RECEPTORS BLT₁ AND BLT₂

Leukotriene B₄ (LTB₄) has been known to induce numerous inflammatory functions in leukocytes, including chemotaxis, degranulation, and adhesion to endothelial surfaces. BLT₁, the first described LTB₄ 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]. BLT₁ 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. BLT₁ binds LTB₄ with high affinity, with K_d ranging from 0.39 to 1.5 nM in human neutrophils and transfected CHO and HEK cells[37], and high specificity, as competitive binding studies show displacement only with 20-hydroxy LTB₄ and 12-epi LTB₄[38]. Initial Northern blotting studies of human tissues displayed highest BLT₁ expression in peripheral blood leukocytes, with lower expression in the spleen and thymus[35]. Protein expression of BLT₁ 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 BLT₁ 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 BLT₁ 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 BLT₁ 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 LTB₄ receptors on neutrophils, one binding LTB₄ 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 LTB₄ receptor, designated BLT₂, was identified in humans and mice based on identification of an open reading frame encoding a seven transmembrane-spanning receptor with sequence similarities to BLT₁[48], which was independently identified and cloned by other groups[49,50,51]. HEK cells transfected with human BLT₂ bind LTB₄ with a K_d of 23 nM, which is 20 times higher than that of human BLT₁[38]. Human BLT₂ also binds and is activated by a broader range of eicosanoids, including 20-hydroxy LTB₄, 12-epi-LTB₄, 12(S)- and 15(S)-hydroxyeicosatetraenoic acid (HETE), and 12(S)- and 15(S)-hydroperxyeicosatetraenoic acid

TABLE 2
BLT₁ and BLT₂ Receptors

	BLT ₁	BLT ₂
Receptor expression on leukocytes	<i>Human:</i> neutrophils, eosinophils, basophils, mast cells, monocytes, CD4 and CD8 cells <i>Mouse:</i> neutrophils, eosinophils, mast cells, monocytes, dendritic cells, activated Th1 and Th2 cells, effector CD8 cells	<i>Human:</i> neutrophils, eosinophils, monocytes, HMC-1 cells (mast cell line), dendritic cells <i>Mouse:</i> 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 BLT₂ and stimulated with LTB₄ demonstrate calcium flux and chemotaxis inhibitable by pertussis toxin[38,48], indicating function as a classical chemoattractant receptor.

Human BLT₂ shares 45.2 and 44.6% homology at the amino acid level with human and mouse BLT₁, respectively, while human and mouse BLT₂ share an even higher degree of homology at 92.7%[48]. Interestingly, the open reading frame of human BLT₂ overlaps with the putative promoter region of the BLT₁ gene[52], initially suggesting that transcription of the two receptors may be linked. However, BLT₁ expression is largely limited to leukocytes, while human BLT₂ 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 BLT₂ is found in resting CD4, CD8, CD19, and CD14 cells[53]. In spite of significant shared homology, mouse BLT₂ differs significantly from human BLT₂ in that it is not ubiquitously expressed, but rather has a more restricted distribution in the small intestine, colon, and keratinocytes[54] (Table 2).

BLT₁ and Neutrophils

LTB₄ was first recognized as a potent stimulator of neutrophil chemotaxis and aggregation. Since then, multiple roles for LTB₄-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, BLT₁ was first identified on granulocyte-like differentiated HL-60 cells[35], and protein expression was later confirmed using BLT₁-specific monoclonal antibodies[57] and presumed to mediate known LTB₄ effects on neutrophils. Some uncertainty remains as to the presence of BLT₂ 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 BLT₂[58].

Mice overexpressing the human BLT₁ receptor demonstrate enhanced neutrophil migration in models of LTB₄-induced skin inflammation and ischemia perfusion[59]. *In vitro* studies utilizing the BLT₁-specific inhibitor CP-105,696 have demonstrated that LTB₄ activation of human neutrophils are mediated through BLT₁, including calcium flux, chemotaxis, CD11b up-regulation, and retardation of apoptosis[60,61]. However, BLT₁ inhibition using U75302 demonstrates residual calcium flux and degranulation when human neutrophils are similarly stimulated with LTB₄, suggesting some BLT₂

involvement in these processes[43]. Treatment of human peripheral neutrophils with dexamethasone enhances BLT₁ expression, as well as calcium flux, chemotaxis, and survival[62]. Treatment with both the BLT₁ inhibitor U75302 and BLT₂ inhibitor LY255283 blocks these effects[62], implying that endogenous production of LTB₄ is critical for these dexamethasone-mediated effects and suggesting an active role for both BLT₁ and BLT₂ on neutrophil function. Stimulation by other mediators may also lead to activation of neutrophil LTB₄ synthesis and autocrine activation, as PAF-induced neutrophil degranulation and chemotaxis are both reduced by inhibition of 5-lipoxygenase activating protein (FLAP) and BLT₁[63].

CP-105,696 is also a functional specific inhibitor of murine BLT₁[64] and has been used to probe BLT₁ 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-1 β -stimulated endothelium[65], suggesting a role for BLT₁ in neutrophil extravasation. CP-105,696 also reduces neutrophil migration in an LTB₄-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 BLT₁/BLT₂ inhibitor, preserves renal function and reduced kidney neutrophil infiltration and structural damage[69].

The generation of BLT₁^{-/-} mice has also highlighted the necessity for BLT₁ in directing neutrophil migration in numerous inflammatory responses. Initial characterization of neutrophils isolated from BLT₁^{-/-} mice displayed eradication of calcium flux, chemotaxis[70,71], and degranulation[72] in response to LTB₄, 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 BLT₁^{-/-} mice compared with wild-type, and BLT₁^{-/-} 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, BLT₁^{-/-} 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 LTB₄[67,74]. These studies show that autocrine activation of BLT₁ on neutrophils is required for BLT₁-deficient neutrophils to be recruited into the joint subsequently, indicating a novel mechanism of autocrine BLT₁-mediated neutrophil activation in the amplification of innate immune responses.

BLT₁ and Eosinophils

LTB₄ 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 BLT₁ and BLT₂ mRNA have been detected in human eosinophils[49], indicating that either of these receptors may mediate these actions. CP-105,696-mediated BLT₁ inhibition diminishes LTB₄-induced calcium flux in human eosinophils[61]; however, further detailed studies of the differential roles of BLT₁ and BLT₂ activation on human eosinophil chemotaxis, aggregation, and degranulation have not yet been described in the literature. Of note, basophils also express BLT₁, but not BLT₂, and IL-3-primed basophils degranulate upon exposure to LTB₄[58].

Murine BLT₁ was first identified using degenerate PCR amplification of eosinophil mRNA with human BLT₁ expression being confirmed on human eosinophils[36], and accordingly, abrogation of BLT₁ function has been shown to lead to attenuated eosinophil migration in various mouse models of inflammation. BLT₁^{-/-} 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 LTB₄, leading to subsequent eosinophil BLT₁-mediated migration. However, eosinophil recruitment after direct injection of CCL11/eotaxin-1 into the pleural space is also diminished by BLT₁ inhibition, although the CCL11/eotaxin-1 injection itself does not increase pleural LTB₄ levels[80], leading the authors to postulate that CCL11/eotaxin-1 induces BLT₁-LTB₄ autocrine activation of eosinophils at a microscopic level necessary for their migration towards CCL11/eotaxin-1 and possibly other chemoattractants as well.

BLT₁ and BLT₂ and Mast Cells

An analysis of mast cell–derived factors that induce chemotaxis of immature murine bone marrow–derived mast cells (BMMCs) identified LTB₄ 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 LTB₄[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 BLT₁ mRNA decreased with murine mast cell maturation and were presumed to be the cause for decreased ability to migrate towards LTB₄, but the specific LTB₄ receptor responsible for mast cell chemotaxis was not confirmed through the use of pharmacologic inhibitors. Another study has subsequently demonstrated message for both BLT₁ and BLT₂ in murine BMMCs and the human mast cell line HMC-1[42]. Increasing the time of incubation in SCF diminishes human mast cell BLT₁ surface expression, suggesting an explanation for the loss of migration to LTB₄ during the maturation of murine BMMCs. However, chemotaxis of both murine BMMCs and HMC-1 cells towards LTB₄ is reduced with either BLT₁ or BLT₂ 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, LTB₄ 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.

BLT₁ and Monocytes

LTB₄ has been shown to activate monocytes and macrophages by inducing chemotaxis, surface CD11b expression, and phagocytosis. Message for both BLT₁ and BLT₂ receptors has been detected in CD14⁺ monocytes[53], and flow cytometric studies of human peripheral blood leukocytes have confirmed BLT₁ expression on CD14⁺⁺CD16⁻ monocytes, which represent 85–90% of the peripheral monocyte population[82]. Both BLT₁ expression and activity are decreased by the addition of inflammatory cytokines such as IFN- γ and TNF, while BLT₁ transcription is elevated by IL-10 and dexamethasone[82]. BLT₁⁺ monocytes also express increased levels of CCR2, a chemokine receptor whose expression is also regulated similarly to BLT₁, implying a cooperative role for BLT₁- and CCR2-mediated signaling and chemotaxis in this inflammatory monocyte subset. Additionally, BLT₁-activated monocytes produce CCL2/MCP-1[83]. These data suggest that BLT₁-stimulated monocytes may amplify further monocyte recruitment by generating CCL2/MCP-1 and promoting subsequent CCR2-mediated chemotaxis.

In mice, BLT₁ 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 LTB₄ production; however, BLT₁ 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 BLT₁ 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].

BLT₁ and T Lymphocytes

Although LTB₄ is characteristically identified as a potent activator of leukocytes of the innate immune system, such as granulocytes and monocytes, LTB₄ 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 BLT₁ receptor led to an exploration of its expression on human peripheral blood leukocytes and its identification on T cells[39,53]. BLT₁ 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 BLT₁ on T cells using mouse models of inflammation has revealed that BLT₁ activation plays a critical role in the recruitment of effector CD4 and CD8 cells early in inflammation. Although BLT₁ is not found in naïve T cells, BLT₁ 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, BLT₁^{-/-} 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 BLT₁-mediated T-cell trafficking in both humoral and adaptive immune responses[89]. Peribronchial lymph node cells from OVA-sensitized BLT₁^{-/-} 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 BLT₁ activation of helper T cells is a critical component of the early allergic response.

Effector CD8 cells also display significantly higher levels of BLT₁ expression compared with central memory CD8 cells and migrate in response to LTB₄ *in vitro* and *in vivo* settings[90,91]. Analysis of mast cell supernatants identify LTB₄ to be the major mast cell-produced chemotactic factor inducing effector CD8 T cell migration[91], and that mast cell- and FcεRI^{-/-} mice produce lower levels of LTB₄ in BAL fluid after OVA sensitization and challenge[92]. Transfer of OVA-primed BLT₁^{-/-} 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 BLT₁ 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 BLT₁. BLT₁ 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 BLT₁^{-/-} CD8 effector cells results in diminished lung inflammation and increased mouse survival, and BLT₁^{-/-} 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 BLT₁^{-/-} T cells results in less severe disease than transfer of T cells from wild-type mice, although there appears to be a BLT₁-dependent contribution to the recruitment of other immune cells such as neutrophils[96].

A detailed characterization of BLT₁ in human resting peripheral blood cells has identified BLT₁ expression on a rare subset of CD3⁺CD4⁺ and CD3⁺CD8⁺ cells (0–1%)[41]. This BLT₁⁺ 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 BLT₁ expression. Asymptomatic atopic asthmatics demonstrate increased numbers of BLT₁⁺ CD4 and CD8 memory T cells in the airways, and EBV-specific CD8 cells from acutely infected individuals also have increased levels of BLT₁ expression compared with those with asymptomatic chronic infection[41]. In addition, patients with bronchiolitis obliterans post lung transplantation express greater numbers of BLT₁⁺ CD4 and CD8 cells in the airways compared with normal transplanted lungs[95]. These studies demonstrate that BLT₁ 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, BLT₁ expression is transiently increased on this T-cell subpopulation, enhancing their ability to quickly respond to the early phases of infectious and inflammatory processes.

BLT₁ and BLT₂ and Dendritic Cells

Murine bone marrow–derived dendritic cells (mBMDCs) migrate in response to LTB₄, an effect abrogated in cells lacking BLT₁[97]. In addition, LTB₄ up-regulates expression of CCR7 and its ligand CCL19/ELC, both of which mediate mBMDC migration to the draining lymph nodes. Accordingly, BLT₁^{-/-}/BLT₂^{-/-} 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 BLT₁ 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 LTB₄ in a PTX-sensitive fashion. However, these cells have been shown to express BLT₂ message and chemotaxis is eliminated by the BLT₂-specific inhibitor LY255283[98]. These studies confirm an active biological role for LTB₄ 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 CYSLT₁ AND CYSLT₂

The cysteinyl leukotrienes (cysLTs), LTC₄, LTD₄, and LTE₄, 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, CysLT₁ and CysLT₂, both seven transmembrane-spanning G-protein receptors. Human CysLT₁ was independently cloned and characterized by two groups[100,101]. CysLT₁ binds preferentially to LTD₄, with 200-fold less affinity for LTE₄ and LTC₄, and cellular calcium mobilization by CysLT₁ 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 CysLT₁ 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 CysLT₁ in lung smooth muscle and macrophages, eosinophils, monocytes, and B cells[103], and CysLT₁ message and signaling are present in human mast cells derived from cord blood as well[104]. CD34⁺ hematopoietic progenitor cells also express CysLT₁ and migrate in response to LTD₄[105]. Transgenic mice overexpressing human CysLT₁ develop enhanced airway eosinophilia, Th2 cytokine production, and airways hyper-responsiveness in a model of *Aspergillus fumigatus* sensitization and challenge[106]. Mouse CysLT₁ bears 87% homology with the human ortholog at the amino acid level and shares similar binding characteristics[107,108,109]. Mice express CysLT₁ 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 CysLT₁ in subcutaneous connective tissue fibroblasts[109] (Table 3). CysLT₁ 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
CysLT₁ and CysLT₂ Receptors

	CysLT ₁	CysLT ₂
Receptor expression on leukocytes	<i>Human:</i> eosinophils, basophils, mast cells, monocytes and macrophages, dendritic cells, B cells, T cells <i>Mouse:</i> macrophages	<i>Human:</i> eosinophils, mast cells, macrophages, dendritic cells, T cells <i>Mouse:</i> 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 CysLT₂ shares 38% amino acid homology with human CysLT₁, and binds LTC₄ and LTD₄ with equal affinity, followed by LTE₄[111,112,113]. Northern Blot and dot blot analysis has detected high levels of human CysLT₂ 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, CysLT₂ message has been identified in HUVECs, levels of which are elevated on IL-4 stimulation or upon reaching confluence[114]. Among leukocytes, human CysLT₂ is expressed on macrophages, eosinophils[111], and mast cells[115]. Mouse CysLT₂ shares 73% sequence homology with human CysLT₂ and 39% homology with mouse CysLT₁, and binds to the same natural ligands as human CysLT₂ with similar affinities[109,116]. Mouse CysLT₂ 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).

CysLT₁ 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 LTC₄ synthase, the enzyme required for CysLT synthesis, have markedly decreased eosinophilic inflammation in an asthma model[117], and selective CysLT₁ inhibition reduces tissue eosinophilia in both murine[118] and human allergic conditions. *In vitro* studies have shown that LTC₄, LTD₄, and LTE₄ induce surface expression of the adhesion molecule Mac-1 (but not LFA-1) and chemotaxis of human peripheral blood eosinophils in a CysLT₁-dependent manner[119,120]. CysLT₁ 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 CysLT₁ activation on eosinophils include promotion of their survival and effector functions. LTD₄ enhances eosinophil differentiation from progenitor cells[122] and promotes mature eosinophil survival[123], of which both processes are CysLT₁ 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 CysLT₁ inhibition[124]. When peripheral blood eosinophils are used, however, LTC₄ and LTD₄ elicit IL-4 release when added to permeabilized eosinophils only, while addition of CysLT₁ and CysLT₂ inhibitors

does not block this release. These findings suggest that in addition to binding CysLT₁, CysLTs may bind novel CysLT intracellular receptors necessary for the transcription and release of inflammatory cytokines[125].

CysLT₁ and Monocytes/Macrophages

Initial characterization of the human CysLT₁ 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 LTD₄ and lipopolysaccharide (LPS) significantly increases macrophage production of CCL3/MIP-1 α , a chemoattractant for eosinophils and monocytes, a response reversible by CysLT₁ inhibition[126]. In this fashion, CysLT activation of macrophages serves as an additional means of inducing eosinophilic inflammation. Of interest is that both LTD₄ 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 CysLT₁ 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 CysLT₁ transcription, surface expression, and chemotaxis towards LTD₄, overall enhancing monocyte participation in the allergic response[127]. IL-4 stimulation of THP-1 cells induces CysLT₁ expression mediated by STAT6 activation, leading to the enhanced production of CCL2/MCP-1[128]. In addition to mediating monocyte chemotaxis towards CysLTs directly, CysLT₁ 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 LTB₄ or LTD₄[129]. These data suggest that CysLT₁ activation of monocytes amplifies Th2-mediated responses, in which Th2 cytokines induce enhanced monocyte responsiveness to LTD₄ and promote the recruitment of monocytes and eosinophils towards sites of inflammation.

CysLT₁ and CysLT₂ and Mast Cells

Mast cells are an integral component of allergic and inflammatory responses, and produce CysLTs on stimulation with IL-4 or Fc ϵ RI cross-linking. Both CysLT₁ and CysLT₂ have been identified in cord blood-derived human mast cells and the human mast cell line HMC-1[115,130,131]. CysLT₁ activation increases human and mouse mast cell proliferation in the presence of IL-4[132]. Unprimed human mast cells respond to LTC₄ and LTD₄ as demonstrated by calcium mobilization, a process primarily mediated through CysLT₁. LTC₄ and LTD₄ also amplify the transcription and release of IL-5, TNF- α , and CCL4/MIP-1 β through ERK- and NFAT/calcineurin-mediated CysLT₁ activation of IL-4-primed mast cells. Mast cell cytokine production resulting from IgE cross-linking of Fc ϵ RI is also partially dependent on autocrine production of CysLTs and subsequent activation of CysLT₁. However, mast cell degranulation and production of histamine and PGD₂ is not affected by CysLT₁ activation[104]. These studies show a role for CysLT₁ 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 CysLT₁ and CysLT₂ 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 pyrimidnergic ligand UDP. Indeed, mast cell CysLT₁ also acts as an active receptor for UDP, as shown by initiation of calcium flux that is blocked by the CysLT₁ inhibitor MK571[130]. UDP activation of CysLT₁ strongly induces the production of TNF- α and CCL4/MIP-1 β in

IL-4-primed mast cells in a manner similar to LTD₄ and LTE₄, but it induces IL-5 less strongly than the CysLTs[104].

Priming of mast cells with IL-4 prior to CysLT₁ stimulation increases calcium mobilization, but it does not affect CysLT₁ receptor cell surface expression[130]. CysLT₂ receptor expression is increased after IL-4 priming, however, accounting for this difference and indicating that this is a functional receptor on mast cells. CysLT₂ regulation and signaling on mast cells also differs from CysLT₁ in other ways. Stimulation with LTC₄ and LTD₄ in the presence of CysLT₁ inhibitor suppresses the production of most cytokines, with the exception of CCL2/MCP-1 and CXCL8/IL-8, indicating that these are induced by CysLT₂ activation alone. Unlike CysLT₁, which has been shown to signal through PTX-insensitive pathways, PTX completely blocks CysLT₂-mediated CXCL8/IL-8 production, a neutrophil-active chemokine[115]. Therefore, CysLT₂ may play a role in innate immune responses by activating mast cell production of a distinct set of chemokines.

CysLT₁ 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 LTD₄ either *in vivo* or *in vitro* reinstates the dendritic cell chemotactic response, indicating that dendritic cells must synthesize LTD₄ and export it out of the cell, where it binds to CysLT₁ receptor in an autocrine manner and induces migration towards CCL19/ELC.

CysLT₁ and CysLT₂ 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 LTD₄ as manifested by decreased calcium flux and chemotaxis[134]. CysLT₁ 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 CysLT₁ than plasmacytoid dendritic cells and would be affected more by CysLT₁ 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. CysLT₁ 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]. CysLT₁ stimulation of MoDCs also induces CXCL8/IL-8 production, pointing to a role for DCs in stimulating innate immune responses as well[137].

CysLT₁ 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 CysLT₁ on stimulation with antigen, although this has been identified only at the mRNA level[138]. CysLT₂ 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 CysLT₁ blockade, IL-12 production is increased[138]. These findings suggest that CysLT₁ 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 CysLT₂ activation of dendritic cell and skewing towards a Th1 response, if CysLT₂ 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].

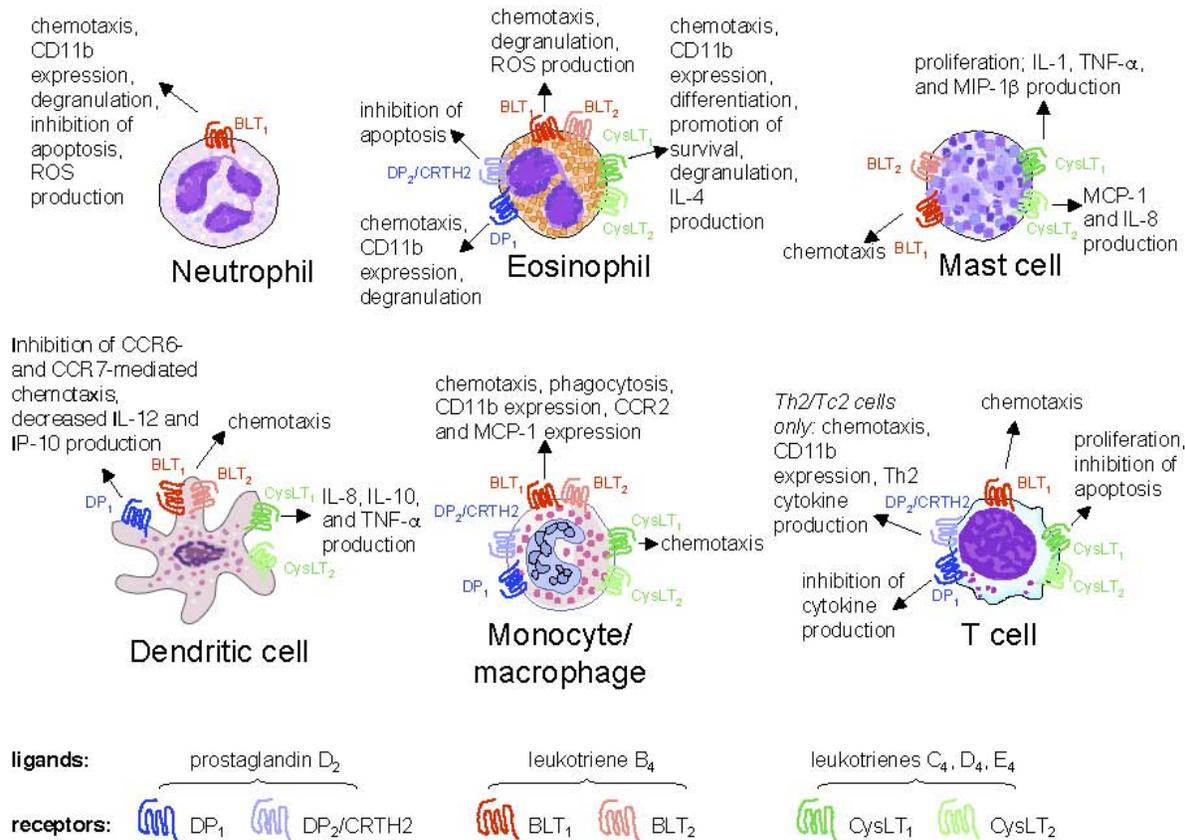


FIGURE 1. Distribution and functions of PGD₂, LTB₄, and CysLT receptors on human leukocyte populations. Leukocyte expression and known functions of DP₁, DP₂/CRTH2, BLT₁, BLT₂, CysLT₁, and CysLT₂ receptors after activation with their respective ligands are depicted. This diagram represents human leukocytes; while mouse and other species have similar distribution and functions, significant differences exist, as described in this review. ROS, reactive oxygen species.

CysLT₁ and Lymphocytes

Resting T cells isolated from the peripheral blood of humans[103] and mice[140] express very low levels of CysLT₁ and CysLT₂. However, murine CysLT₁ 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 LTD₄[140]. One study demonstrated that only 0.7 and 2.5% of resting human T cells express CysLT₁ and CysLT₂, respectively, but incubation with IL-4 and IL-13 increases CysLT₁ and CysLT₂ 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 CysLT₁ 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 CysLT₁ and CysLT₂, but only CysLT₁ expression is increased after stimulation with IL-4 and either anti-CD40 or CD154-transfected fibroblasts. CysLT₁ activation by LTD₄ 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.

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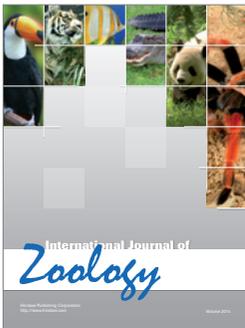
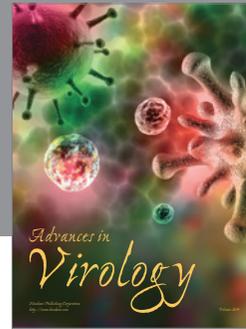
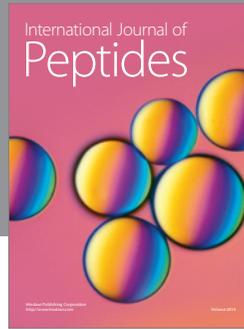
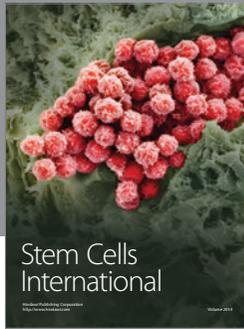
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