

International Union of Basic and Clinical Pharmacology. LXXXIV: Leukotriene Receptor Nomenclature, Distribution, and Pathophysiological Functions

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Abstract—The seven-transmembrane G protein-coupled receptors activated by leukotrienes are divided into two subclasses based on their ligand specificity for either leukotriene B₄ or the cysteinyl leukotrienes (LTC₄, LTD₄, and LTE₄). These receptors have been designated BLT and CysLT receptors, respectively, and a subdivision into BLT₁ and BLT₂ receptors and CysLT₁ and CysLT₂ receptors has been established. However, recent findings have also indicated the existence of pu-

tative additional leukotriene receptor subtypes. Furthermore, other ligands interact with the leukotriene receptors. Finally, leukotrienes may also activate other receptor classes, such as purinergic receptors. The aim of this review is to provide an update on the pharmacology, expression patterns, and pathophysiological roles of the leukotriene receptors as well as the therapeutic developments in this area of research.

I. Introduction: Leukotriene Receptors

The seven-transmembrane G protein-coupled receptors (GPCRs¹) activated by leukotrienes are divided into two subclasses based on their ligand specificity for either

leukotriene B₄ (LTB₄) or the cysteinyl leukotrienes (LTC₄, LTD₄, and LTE₄). The leukotriene receptors belong to the A5 subfamily of the rhodopsin receptor-like GPCRs (Joost and Methner, 2002). According to the

previous report from the International Union of Basic and Clinical Pharmacology's (IUPHAR) Nomenclature Committee for Leukotriene Receptors, these receptors have been designated BLT and CysLT receptors, respectively (Brink et al., 2003). Furthermore, a subdivision into BLT₁ and BLT₂ receptors and CysLT₁ and CysLT₂ receptors has been established, as indicated in Table 1 (Brink et al., 2003).

However, several reports have also indicated the existence of additional leukotriene receptor subtypes (Rovati et al., 1997; Bäck, 2002; Norel and Brink, 2004; Rovati and Capra, 2007; Austen et al., 2009). In addition, evidence has emerged that ligands other than leukotrienes interact with the leukotriene receptors and

that leukotrienes may also signal through receptors preferentially activated by other endogenous ligands. For example, lipid mediators that are structurally different from leukotrienes have been reported to signal through BLT receptors (Arita et al., 2007; Okuno et al., 2008). As described later, 12(*S*)-hydroxyheptadeca-5*Z*,8*E*,10*E*-trienoic acid (12-HHT) was identified as a more potent ligand for BLT₂R than for LTB₄ (Okuno et al., 2008). Furthermore, although evidence that LTE₄ signals through the P2Y₁₂ receptor was demonstrated (Nonaka et al., 2005; Paruchuri et al., 2009; Fredman et al., 2010), one of the orphan GPCRs, GPR17, has been postulated to be activated by both cysteinyl leukotrienes and nucleotides (Ciana et al., 2006). Finally, both the CysLT₁ receptor (CysLT₁R) antagonists in clinical use as antiasthmatic drugs have been demonstrated to inhibit the effects of nucleotides acting at different P2Y receptors. These observations demonstrate that these classic leukotriene receptor antagonists (LTRAs) can inhibit non-CysLT₁-mediated proinflammatory reactions, suggesting activities potentially relevant for interpatient variability in response to treatment. The aim of the present review is to provide an extensive update on the pharmacology, expression patterns, and pathophysiological roles of the leukotriene receptors. Furthermore, a comment on the potential therapeutic developments in this area of research will be presented.

A. Brief Historical Background of Leukotrienes and Their Receptors

Ever since the identification of the biochemical structure of the leukotrienes and their association with inflammation (Samuelsson, 1983), the pathophysiological role of these lipid mediators has been explored in many experimental approaches (Brink et al., 2003). Initially, LTB₄ was appreciated for its potent chemotactic effects on neutrophil granulocytes (Ford-Hutchinson et al., 1980; Malmsten et al., 1980; Palmblad et al., 1981) and its ability to serve as a complete secretagogue for human peripheral blood neutrophils (Serhan et al., 1982). In contrast, initial studies of cysteinyl leukotrienes were mainly focused on their potent bronchoconstrictive effects (Dahlén et al., 1980). However, subsequent studies have extended these findings and associated leukotriene receptor signaling with several pathophysiological processes.

The first leukotriene receptor to be cloned was the human BLT₁, and the molecular structure was reported in 1997 (Yokomizo et al., 1997). This molecular identification of the BLT₁ receptor (BLT₁R) permitted the characterization of functional BLT₁R in several leukocyte populations (Kim and Luster, 2007) and also in nonmyeloid cells, such as vascular smooth muscle and endothelial cells (Bäck et al., 2005). Although the LTB₄-induced interaction with BLT₁R corresponded with several effects observed in those target cells, initial studies had revealed both high- and lower-affinity binding sites for LTB₄ specifically in human granulocytes (Goldman and Goetzl, 1984). The molecular

¹Abbreviations: β_2 AR, β_2 -adrenoreceptor(s); aa, amino acids; AD, atopic dermatitis; AIA, aspirin-induced asthma; AML1, acute myeloid leukemia 1; AP-1, activator protein-1; AR, allergic rhinitis; ATA, aspirin-tolerant asthma; BAL, broncho-alveolar lavage; BAY U9773, 6(*R*)-(4-carboxyphenylthio)-5(*S*)-hydroxy-7(*E*),9(*E*),11(*Z*),14(*Z*)-eicosatetraenoic acid; BLTR, BLT receptor(s); BLT₁R, BLT₁ receptor(s); BLT₂R, BLT₂ receptor(s); BMDC, bone marrow-derived dendritic cell; BMMC, bone marrow-derived mast cell; CF, cystic fibrosis; CHO, Chinese hamster ovary; COPD, chronic obstructive pulmonary disease; COX, cyclooxygenase; CP-105,696, 1-[3-(4-phenyl-benzyl)-4-hydroxy-chroman-7-yl] cyclopentane carboxylic acid; CU, chronic urticaria; CVD, cardiovascular disease; CysLTR, cysteinyl leukotriene receptor(s); CysLT₁R, CysLT₁ receptor(s); CysLT₂R, CysLT₂ receptor(s); DC, dendritic cell; DSS, dextran sodium sulfate; EAE, allergic encephalomyelitis; EC, endothelial cell; ECP, eosinophil cationic protein; EGFR, epidermal growth factor receptor; ERK, extracellular signal-regulated kinases; FcR, Fc receptor; FLAP, 5-lipoxygenase activating protein; GPCR, G protein-coupled receptor; GRK, GPCR kinases; h, human; HEK, human embryonic kidney; HETE, hydroxyeicosatetraenoic acid; HHT, hydroxyheptadecatrienoic acid; HpETE, hydroperoxyeicosatetraenoic acid; HUVEC, human umbilical cord endothelial cell; IBD, inflammatory bowel disease; IFN, interferon; IGF, insulin growth factor; IL, interleukin; IUPHAR, International Union of Basic and Clinical Pharmacology; JNK, c-Jun NH₂-terminal kinase; 5-LO, 5-lipoxygenase; LPS, lipopolysaccharide; LT, leukotriene; LTC₄S, LTC₄ synthase; LTRA, leukotriene receptor antagonist; LY255283, 1-[5-ethyl-2-hydroxy-4-[[6-methyl-6-(1*H*-tetrazol-5-yl)heptyl]oxy]phenyl]ethanone; LY293111, 2-[2-propyl-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]propoxy]phenoxy]benzoic acid; m, murine; MAPK, mitogen-activated protein kinase; MC, mast cell; MCP, monocyte chemoattractant protein; MIP, macrophage inflammatory protein; MK0571, 3-[[3-[2-(7-chloroquinolin-2-yl)vinyl]phenyl]-(2-dimethylcarbamoyl-ethylsulfanyl)methylsulfanyl] propionic acid; MMP, matrix metalloproteinases; MNC, mononuclear cell; MRS 2395, 2,2-dimethyl-propionic acid 3-(2-chloro-6-methylaminopurin-9-yl)-2-(2,2-dimethyl-propionyl-oxy-methyl)-propyl ester; MS, multiple sclerosis; NCBI, National Center for Biotechnology Information; NF- κ B, nuclear factor κ B; NO, nitric oxide; NSAID, nonsteroidal anti-inflammatory drug; OVA, ovalbumin; P2Y, pyrimidineric nucleotide; PAF, platelet-activating factor; PGE₂, prostaglandin E₂; PI, phosphatidylinositol; PI3K, phosphatidylinositol 3-kinase; PK, protein kinase; PPAR, peroxisome proliferator-activated receptor; PTX, pertussis toxin; QL, quality of life; RANTES, regulated on activation normal T cell expressed and secreted; RT-PCR, reverse transcriptase-polymerase chain reaction; Rv, resolvin; SKF 104353, 2(*S*)-hydroxyl-3(*R*)-carboxyethylthio)-3-[2-(8-phenyloctyl) phenyl] propanoic acid; SMC, smooth muscle cell; SNP, single nucleotide polymorphism; STAT, signal transducer and activator of transcription; Th, T helper; TM, transmembrane domain; TNF, tumor necrosis factor; TRP, transient receptor potential; U75302, -[6-(3-hydroxy-1*E*,5*Z*-undecadienyl)-2-pyridinyl]-1,5-hexanediol; VEGF, vascular endothelial growth factor; WT, wild type.

TABLE 1
Leukotriene receptors

For full details, see <http://www.iuphar-db.org/DATABASE/ObjectDisplayForward?objectId=270&familyId=35>.

Receptor	BLT ₁	BLT ₂	CysLT ₁	CysLT ₂
Amino acids				
<i>Hs</i>	352	389	337	346
<i>Mm</i>	351	360	339	309
<i>Rn</i>	351	358	352	309
NCBI sequence no.				
<i>Hs</i>	NP_858043	NP_062813	NP_006630	NP_065110
<i>Mm</i>	NP_032545	NP_065236	NP_067451	NP_598481
<i>Rn</i>	NP_067688	NP_446092	NP_446093	NP_596904
Gene name				
<i>Hs</i>	<i>LTB4R</i>	<i>LTB4R2</i>	<i>CYSLTR1</i>	<i>CYSLTR2</i>
<i>Mm</i>	<i>Ltb4r1</i>	<i>Ltb4r2</i>	<i>Cysltr1</i>	<i>Cysltr2</i>
<i>Rn</i>	<i>Ltb4r</i>	<i>Ltb4r2</i>	<i>Cysltr1</i>	<i>Cysltr2</i>
Chromosomal location				
<i>Hs</i>	14q11.2-q12	14q11.2-q12	Xq13.2-21.1	13q14.12-q21.1
<i>Mm</i>	14 C2	14 C1	X D	14 D2
<i>Rn</i>	15p 13	15p 13	Xq 31	15p 11
Selective ligands	— ^a	— ^a	— ^a	— ^a
Nonselective ligands	LTB ₄	LTB ₄ ; 12-HHT	LTC ₄ ; LTD ₄ ; LTE ₄	LTC ₄ ; LTD ₄ ; LTE ₄
Selective antagonists	U75302; CP-105,696	LY-255,283	Montelukast; zafirlukast; pranlukast	CysLT2cpd
Nonselective antagonists	ONO-4057	ONO-4057	BAY U9773	BAY U9773

Hs, *Homo sapiens*; *Mm*, *Mus musculus*; *Rn*, *Rattus norvegicus*; ONO-4057, (5-[2-(2-carboxyethyl)-3-[6-(4-methoxyphenyl)-5*E*-hexenyl]oxyphenoxy]valeric acid.
^a No ligands identified.

explanation for the latter finding was provided in 2000, when a gene with high sequence similarity to BLT₁R was identified and encoded a low-affinity LTB₄ receptor, which has subsequently been denoted BLT₂R (Yokomizo et al., 2000; Brink et al., 2003). Transgenic overexpression of the human BLT₁R in mice increased the inflammatory response to LTB₄ (Chiang et al., 1999), whereas genetic BLT₁R disruption decreased leukocyte chemotaxis and protected against disease development in response to several different proinflammatory stimuli (Haribabu et al., 2000; Tager et al., 2000; Brink et al., 2003) (see section II.E).

The classification of the CysLT receptors was initially based on the differential profiles of guinea pig trachea contractions induced by either LTC₄ or LTD₄ (Brink et al., 2003). Because a classification based on agonist selectivity is not generally applicable, the names CysLT₁ and CysLT₂ were introduced when referring to responses being sensitive and resistant (Labat et al., 1992) to the class of CysLT receptor antagonists, which had been developed for the treatment of asthma (Brink et al., 2003). The subsequent cloning of these receptors in 1999 and 2000 (Lynch et al., 1999; Sarau et al., 1999; Heise et al., 2000; Nothacker et al., 2000; Takasaki et al., 2000) largely confirmed these pharmacological characteristics of the CysLT₁ and CysLT₂ receptors.

B. Chemical Structure of Endogenous Leukotriene Receptor Agonist

Most endogenous ligands for the leukotriene receptors are derived from lipoxygenase metabolism of arachidonic acid and are shown in Fig. 1. The formation of leukotrienes by 5-lipoxygenase (5-LO) involves the oxygenation at carbon number 5 of arachidonic acid to form 5-hydroperoxyicosatetraenoic acid (HpETE). Subsequently, removal of hydrogen at carbon 10 from 5-HpETE leads to formation of

the epoxide intermediate LTA₄, which serves as precursor for LT synthesis (Shimizu et al., 1984; Rådmark and Samuelsson, 2009) (Fig. 1). Although detected in the cytosolic or nucleosolic fraction of resting cells, cellular activation leads to 5-LO translocation to the nuclear envelope in a calcium-dependent manner, where colocalization with the 5-LO-activating protein (FLAP) is a prerequisite for LT synthesis (Evans et al., 2008).

The enzyme LTA₄ hydrolase is located in the cytosol and stereospecifically adds water to carbon 12 of LTA₄, leading to formation of LTB₄ (Haeggström, 2004). Several inactivating pathways for LTB₄ are known, of which ω -oxidation has been most extensively studied in human leukocytes (for review, see Yokomizo et al., 2001b). In this pathway, LTB₄ is converted to 20-hydroxy-LTB₄ by LTB₄ ω -hydroxylase and then to 20-carboxy-LTB₄ as indicated in Fig. 1 (Yokomizo et al., 2001b). The latter metabolites may also act as ligands at the BLT receptors, which will be discussed below.

The other metabolic pathway of LTA₄ involves the enzyme LTC₄ synthase (LTC₄S), a microsomal glutathione transferase, which conjugates LTA₄ with glutathione to form LTC₄ (Fig. 1) (Austen, 2007). After transportation to the extracellular space by an ATP-dependent transporter (multidrug resistance-associated protein) that recognizes its glutathione moiety, LTC₄ is metabolized by γ -glutamyl transpeptidase into LTD₄. Subsequently, a serum dipeptidase, which cleaves the peptide bond between the cysteinyl and glycyl residues in the LTD₄ side chain, leads to the formation of LTE₄ (Fig. 1). Because LTC₄, D₄, and E₄ all contain a cysteinyl group at carbon number 6 (Fig. 1), these LTs are referred to as the cysteinyl leukotrienes. Thus, the receptors for these LTs are termed CysLT receptors (Brink et al., 2003).

In addition to 5-LO metabolites, products of the 12- and 15-lipoxygenase metabolism of arachidonic acid metabo-

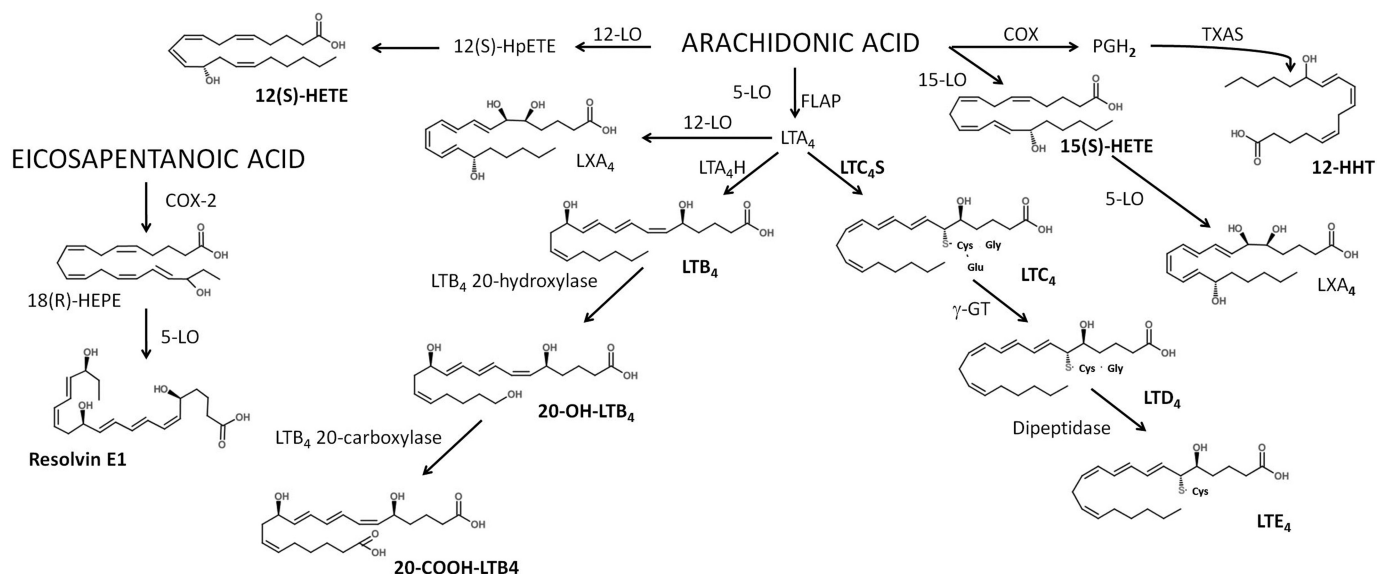


FIG. 1. Biosynthesis and chemical structures of endogenous leukotriene receptor agonists, derived from arachidonic acid. Lipoxin (LX) biosynthesis pathways in humans via 15-LO and 5-LO interaction or 12-LO via 5-LO derived LTA_4 are also depicted. In addition, resolvin E1, derived from eicosapentaenoic acid (EPA), may act as a partial BLT_1R agonist. GT, glutamyl transferase; HEPE, hydroxyeicosapentaenoic acid; LTA_4H , LTA_4 hydrolase; TXAS, thromboxane synthase.

lism can act as ligands for the LT receptors (Fig. 1). For example, 12(*R*)-hydroxyeicosatetraenoic acid (HETE) competes with LTB_4 binding at BLT_1R (Yokomizo et al., 1997, 2001c), whereas 12(*S*)-HETE, 12(*S*)-HpETE, and 15(*S*)-HETE activate BLT_2R (Yokomizo et al., 2001c). The orphan receptor GPR31 has been suggested as a high-affinity receptor for 12(*S*)-HETE (Guo et al., 2011). Finally, 12-HHT (Fig. 1), which is formed through the cyclooxygenase pathway of arachidonic acid metabolism is a high-affinity BLT_2R agonist (Okuno et al., 2008).

II. BLT Receptors

A. BLT Receptor Subtypes

1. *BLT₁ Receptor*. The open reading frame of the human *LTB4R* gene encodes the BLT_1R . The BLT_1R protein

consists of 352 aa (NCBI Reference Sequence: NP_858043) (Fig. 2). The BLT_1R has also been isolated in other species, with a homology similar to that of the human protein in mice (78%; Huang et al., 1998), in guinea pigs (78%; Masuda et al., 1999), and in rats (80%; Toda et al., 1999).

Although LTB_4 seems to be the sole full agonist at BLT_1R , binding studies in membrane fractions of BLT_1R -transfected cells have shown significant competitions for 20-OH- LTB_4 , 12-oxo- LTB_4 and 12-epi- LTB_4 , 20-COOH- LTB_4 , and 12(*R*)-HETE (Yokomizo et al., 1997, 2001c). However, not all of these ligands seem to induce similar intracellular signaling. For example, studies of the recombinant guinea pig BLT_1R have shown that although 20-OH- LTB_4 was less potent than LTB_4 in the mobilization of intracellular Ca^{2+} ($[Ca^{2+}]_i$),

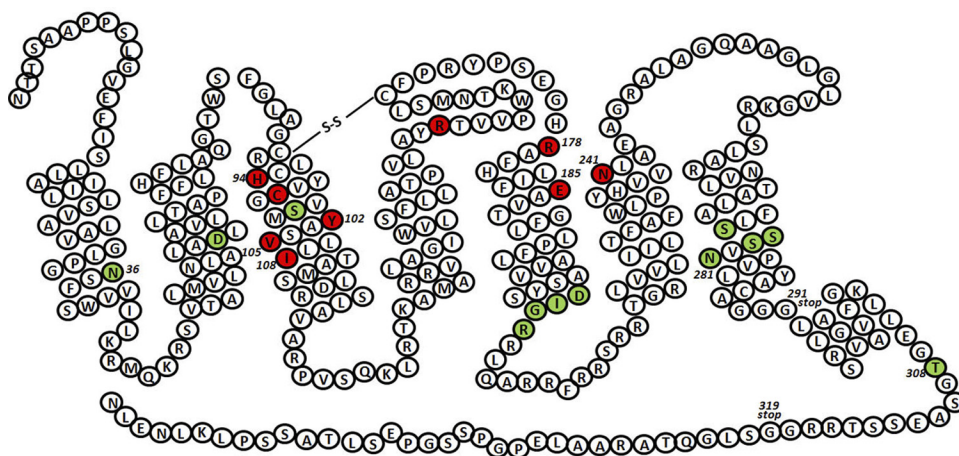


FIG. 2. Schematic representation of the human BLT_1 receptor with the boundaries of each transmembrane, extracellular, and intracellular domain derived from the molecular modeled structure described previously (Basu et al., 2007; Kuniyeda et al., 2007). The amino acid residues involved in the ligand binding are shown in red, whereas residues implicated in receptor signaling are shown in green. The C-tail truncations in the described mutants (see text) are indicated by "stop".

these agonists were equally potent in inhibiting cAMP formation (Masuda et al., 1999). In addition, the eicosapentaenoic acid metabolite resolvin (Rv) E1 was identified as a partial BLT₁R agonist. In particular, RvE1 selectively inhibited adenylate cyclase and attenuated LTB₄-induced nuclear factor κ B (NF- κ B) activation in BLT₁- but not in BLT₂-transfected cells, whereas in human peripheral blood mononuclear cells RvE1 partially induced calcium mobilization and blocked subsequent stimulation by LTB₄ (Arita et al., 2007). These data thus suggest that this mediator, besides activating the receptor ChemR23, could act through inhibition of LTB₄-induced signaling. More information on this new genus of specialized proresolving mediators has been published recently (Bannenberg and Serhan, 2010).

Initially, BLT₁R expression was reported to be restricted to phagocytic leukocytes (Yokomizo et al., 1997), and subsequent studies identified BLT₁R expression in granulocytes, monocytes, and dendritic cells. In addition, lymphocytes also express BLT₁R (see section II.D), and functional BLT₁R are now known to be expressed in nonmyeloid cells, such as vascular smooth muscle cells (SMCs) (Bäck et al., 2005), as well as endothelial cells (ECs) (Qiu et al., 2006), skeletal muscle satellite cells (Sun et al., 2009), and neural stem cells (Wada et al., 2006).

2. BLT₂ Receptor. In the analysis of human and mouse *LTB4R* genes, an open reading frame encoding a putative seven-transmembrane-type receptor with sequence similarities to BLT₁R was identified (Yokomizo et al., 2000). This gene was shown to encode a receptor protein that exhibited LTB₄ binding with a 20-fold higher K_d , and calcium signaling with a 30-fold higher EC₅₀ value compared with BLT₁R (Yokomizo et al., 2000). The gene has been designated *LTB4R2*, and the receptor has been classified as the BLT₂ receptor (BLT₂R) (Brink et al., 2003). The BLT₂R protein consists of 358 aa (NCBI Reference Sequence: NP_062813) and exhibits a 36 to 45% aa identity with the human BLT₁R (Kamohara et al., 2000; Tryselius et al., 2000; Yokomizo et al., 2000). The murine BLT₂R has a 92% aa homology with the human receptor protein, which is a higher homology compared with that of BLT₁R (78% aa identity between murine and human proteins; Iizuka et al., 2005). These data suggest that the BLT₂R has been conserved during evolution.

In contrast to the relatively specific binding of LTB₄ at BLT₁R, several lipoxygenase products in addition to LTB₄ have been identified as ligands for BLT₂R. These include 12(S)-HETE, 12(S)-HpETE, and 15(S)-HETE (Fig. 1) (Yokomizo et al., 2001c). Furthermore, the thromboxane synthase product 12-HHT formed in activated blood platelets and macrophages from prostaglandin H₂ (Fig. 1) is also a natural ligand for BLT₂R (Okuno et al., 2008). In the latter study, the EC₅₀ values of 12-HHT and LTB₄ for [Ca²⁺]_i mobilization in CHO-BLT₂R cells were 19 and 142 nM, respectively, whereas

12-HHT failed to induce calcium mobilization in CHO-BLT₁R cells (Okuno et al., 2008). Several binding studies further demonstrated that BLT₂R is a high-affinity receptor for 12-HHT and that 12-HHT and LTB₄ occupy the same binding site on BLT₂R (Okuno et al., 2008). A synthetic selective BLT₂R agonist has also been reported and termed compound A (Iizuka et al., 2005).

In CHO cells expressing the human BLT₂R, maximal chemotaxis was observed at LTB₄ concentrations greater than 1 μ M, compared with 10 nM for CHO cells expressing human BLT₁R (Yokomizo et al., 2001a; Okuno et al., 2008). Data suggest that coexpression of both human BLT₁ and BLT₂ receptors makes CHO cells migrate toward both very low and high LTB₄ concentrations (Yokomizo et al., 2001a). Other hydroxyeicosanoids acting as BLT₂R agonists, such as 12(S)-HETE, 12(R)-HETE, and 12-epi-LTB₄, require even higher concentrations (approximately 10 μ M) to induce a maximal chemotactic response (Yokomizo et al., 2001c). In contrast, maximal chemotaxis for 12-HHT in CHO cells expressing the human BLT₂R is observed at 30 nM, suggesting that this high-affinity BLT₂R ligand is coupled to chemotaxis (Okuno et al., 2008). In line with findings in CHO cells, murine BLT₂R-expressing 300.19 cells exhibit higher affinity for 12-HHT than for LTB₄. 12-HHT-induced intracellular calcium flux with the same efficacy as LTB₄ (Mathis et al., 2010). However, in the latter cells, 12-HHT was only a weak agonist for chemotaxis with 3% activity relative to LTB₄ (Mathis et al., 2010), suggesting a ligand-specific coupling to chemotaxis. Studies of primary cells have generated variable results as to the role of BLT₂R in LTB₄-induced chemotaxis (see section II.D).

The most abundant BLT₂R expression is found in the spleen, followed by liver, ovary, and leukocytes, and BLT₂R expression is also detected in several other organs, suggesting a ubiquitous expression pattern, at least in human tissues (Yokomizo et al., 2000). The tissue distribution of BLT₂R is different in mouse tissues, with the highest expression in small intestine followed by colon and skin (Iizuka et al., 2005). Physiological and pathophysiological responses associated with BLT₂R signaling include macrophage and mast cell (MC) chemotaxis (Subbarao et al., 2004; Lundeen et al., 2006; Okuno et al., 2008), guinea pig lung parenchyma contraction (Sakata et al., 2004), and mouse models of angiogenesis (Kim et al., 2009), itch-associated scratching (Kim et al., 2008), colitis (Iizuka et al., 2010), and arthritis (Mathis et al., 2010).

3. Genomic Organization and Transcriptional Regulation. The genes encoding BLT₁R and BLT₂R are designated *LTB4R* and *LTB4R2*, respectively (Table 1), and are located within 10 kilobase pairs of each other in both the human and murine genome (Yokomizo et al., 2000). The genes encoding the BLT receptors form a gene cluster on human chromosome 14q11.2-q12 with the open reading frame of the *LTB4R2* gene overlapping one of

the promoter regions of the human *LTB4R* gene (Kato et al., 2000; Yokomizo et al., 2000; Brink et al., 2003). The *LTB4R* gene consists of three exons, and, in line with other receptors for chemoattractants such as fMet-Leu-Phe and interleukin (IL)-8, the open reading frame is intronless (Kato et al., 2000). One of the *LTB4R* promoters has been shown to contain consensus sequence for NF- κ B and Sp1 binding (Kato et al., 2000). Spontaneous mutations around the *LTB4R* and *LTB4R2* genes have been reported to be associated with cerebrovascular disease (Bevan et al., 2008), but the close proximity of the genes encoding those receptors suggests that those polymorphisms cannot be ascribed to either of the genes alone.

In THP-1 cells, the deletion of a Sp1 binding site in the *LTB4R* promoter decreases transcriptional activity (Kato et al., 2000). In human monocytes, BLT₁R mRNA expression is down-regulated by proinflammatory stimuli, such as lipopolysaccharide (LPS), interferon (IFN)- γ , and tumor necrosis factor (TNF)- α , whereas the anti-inflammatory cytokine IL-10 and dexamethasone up-regulate BLT₁R mRNA in these cells (Pettersson et al., 2005). Likewise, in human neutrophil granulocytes, BLT₁R mRNA is up-regulated by dexamethasone (Stankova et al., 2002), and BLT₁R protein and LTB₄ binding are decreased by TNF- α and LPS (O'Flaherty et al., 1991; Pettersson et al., 2003). The latter findings support earlier studies demonstrating decreased LTB₄ binding and LTB₄-induced chemotaxis in neutrophils derived from endotoxemic rabbits (Hartiala et al., 1985; Goldman et al., 1986). Of interest, the transcriptional regulation of the *LTB4R* gene may vary between cells of hematopoietic and nonhematopoietic origin (Kato et al., 2000). In contrast to findings in leukocytes, BLT₁R expression is up-regulated by LPS, IL-1 β , and IFN- γ in vascular SMCs, as demonstrated by studies of cells derived from human, rat, or mouse vessels (Bäck et al., 2005; Heller et al., 2005). Furthermore, vascular injury in vivo significantly up-regulates BLT₁R mRNA through NF- κ B signaling (Bäck et al., 2005). Likewise, whereas BLT₁R is expressed at low levels in human umbilical cord endothelial cells (HUVECs) under resting conditions, either LPS or IL-1 β induces BLT₁R mRNA and protein levels and renders HUVECs responsive to LTB₄ (Qiu et al., 2006). This cell-specific expression of BLT₁R may be dependent on epigenetic regulation, for example, through methylation of the promoter region, which has been shown to regulate BLT₁R transcription in vitro (Kato et al., 2000). In a recent study, the enhancer in the human *LTB4R*, termed *AE-BLex*, was discovered at the intron I-exon-II boundary (Hashidate et al., 2010). *AE-BLex* possesses two acute myeloid leukemia 1 (AML1, also known as Runx1) recognition sites. The AML1/*AE-BLex* complex was confirmed in several BLT₁R-expressing leukemia cell lines and human peripheral leukocytes. Thus, AML1 enhances BLT₁R expression by binding to *AE-BLex*, which is accessible in leukocytes.

The enhancement of the BLT₁R expression in leukocytes is due to a loosening of the chromatin structure around *AE-BLex*, leading to the incremental binding of AML1 (Hashidate et al., 2010).

B. Structure-Function Relationships for BLT Receptors

LTB₄ binds near the extracellular surface of BLT₁R, and although polar residues within transmembrane domains (TMs) III, V, and VI and extracellular loop 2 are critical for ligand binding, polar residues in TMs II, III, and VII play a central role in transducing the ligand-induced conformational change to activation (Sabirsh et al., 2006; Basu et al., 2007) (Fig. 2). Furthermore, a conformational change of TM IV takes place during ligand binding (Baneres et al., 2003).

Site-directed mutagenesis has revealed several of the residues involved in LTB₄ binding to BLT₁R (Fig. 2). Although initial studies had suggested that mutating all receptor cysteines (except Cys⁹⁰ and Cys¹⁶⁸) to serine did not alter ligand binding, selective replacement of Cys⁹⁷ in the TM III domain to serine leads to a 100-fold decrease in the affinity for the agonist (Mesnier and Banères, 2004). Furthermore, residues His⁹⁴, Tyr¹⁰², Val¹⁰⁵, and Ile¹⁰⁸ in TM III, Asn²⁴¹ in TM IV, and Arg¹⁷⁸ and Glu¹⁸⁵ in TM IV have been shown to be necessary for ligand binding (Sabirsh et al., 2006; Basu et al., 2007) (Fig. 2). In addition to the TM domains, the second extracellular loop of BLT₁R may play an even more critical role for LTB₄ binding as suggested by the complete loss of ligand binding after mutation of Arg¹⁵⁶ to alanine (Basu et al., 2007) (Fig. 2). In line with the homology between the BLT₁ and BLT₂ receptors (see section II.A), most of the binding site residues described above suggest a common binding mode for LTB₄ at the two BLT receptor subtypes (Basu et al., 2007). However, the presence of Tyr⁹⁴ in BLT₂R at the place of His⁹⁴ within BLT₁R has been suggested to account for some of the differences in the binding affinities and agonist selectivity between these receptors (Basu et al., 2007).

Structural models for the ligand-free and ligand-bound states of BLT₁R have revealed an activation core formed around Asp⁶⁴, and mutagenesis toward Asn³⁶, Ser¹⁰⁰, and Asn²⁸¹ and a triad of serines, Ser²⁷⁷, Ser²⁷⁸, and Ser²⁷⁹ (Fig. 2), resulted in loss of signaling capacity, whereas mutant receptors retained normal LTB₄ binding (Basu et al., 2007). Furthermore, mutating the third intracellular loop, which consists of the cytoplasmic end of TM V (Fig. 2), reduced G_i-dependent signaling associated with a loss of the high-affinity LTB₄ binding state (Kuniyeda et al., 2007).

The C-tail containing a putative cytoplasmic helical domain, helix 8, of the BLT receptors has recently received attention. For example, BLT₁R with a mutated helix 8 exhibit increased LTB₄ binding as well as prolonged [Ca²⁺]_i mobilization and cellular metabolic activation compared with the WT receptor, suggesting that helix 8 might work as a scaffold for G proteins, changing

BLT₁R to a low-affinity state leading to release of the ligand and signal shutdown (Okuno et al., 2003). In contrast, helix 8 may not be critical for either ligand binding or activation of BLT₂R (Yasuda et al., 2009). However, human BLT₂Rs lacking helix 8 accumulate in the endoplasmic reticulum, suggesting that helix 8 may be required for BLT₂R protein folding and passage through the endoplasmic reticulum to the cell membrane (Yasuda et al., 2009).

Whereas cells expressing a complete C-tail-truncated BLT₁R (G291stop, Fig. 2) exhibit increased numbers of binding sites and increased signal transduction compared with wild-type BLT₁R (Gaudreau et al., 2004), a partially C-tail-truncated BLT₁R mutant (G319stop, Fig. 2) has shown binding characteristics similar to WT BLT₁R (Gaudreau et al., 2002). Furthermore, mutating a dileucine motif (Leu³⁰⁴-Leu³⁰⁵), suggested to be involved in a hydrophobic core (Fig. 2), mimicked the increased binding and signaling associated with the complete C-tail truncated receptor (Gaudreau et al., 2004). In addition, this latter mutation prevented LTB₄-induced BLT₁R internalization (Gaudreau et al., 2004), which corroborated the findings that the complete C-tail-truncated BLT₁R lost the capacity to internalize through the involvement of GPCR kinases (GRK) 2 and 6 (Gaudreau et al., 2002; Chen et al., 2004). In addition, substitution of Thr³⁰⁸ within a putative casein kinase 2 site in the full-length BLT₁R (Fig. 2) prevented most of GRK6-mediated inhibition of LTB₄-induced inositol phosphate production while only partially affecting the LTB₄-induced BLT₁R phosphorylation (Gaudreau et al., 2002). Through the substitution of all Ser and Thr residues in the C-terminal tail with Ala (to generate a phosphorylation-defective mutant) or with Asp/Glu (to mimic constitutive phosphorylation), it has been shown that BLT₁R phosphorylation may be an important mediator of G protein activation, whereas β -arrestin-associated BLT₁R internalization seems to be independent of phosphorylation (Jala et al., 2005). For the murine BLT₁R, a PKC consensus phosphorylation site has been reported to be located on the second intracellular loop, and a Ser¹²⁷ substitution within this site prevented mBLT₁R desensitization (Mollerup et al., 2007).

C. Intracellular Signaling Pathways and Second-Messenger Systems

The downstream intracellular signaling pathways after BLT₁ and BLT₂ receptor activation involve increased [Ca²⁺]_i and inhibition of adenylyl cyclase (Brink et al., 2003). The G protein coupling for the BLT receptors may depend on the type of G proteins expressed in the different cells studied. In several cell types expressing endogenous BLT receptors, pertussis toxin (PTX) inhibits the increased [Ca²⁺]_i in response to LTB₄, suggesting coupling to G_i proteins (Brink et al., 2003). However, in BLT₁R-transfected cells, a significant portion of the LTB₄-induced [Ca²⁺]_i response is resistant to PTX, sug-

gesting also the involvement of G_q-protein coupling (Yokomizo et al., 1997; Haribabu et al., 1999; Brink et al., 2003; Sabirsh et al., 2004). These different profiles of PTX sensitivity suggest that BLT₁R and BLT₂R signal through different subtypes of G_i proteins (Yokomizo et al., 2000).

BLT receptor transduction also activates a number of kinases that phosphorylate downstream signal transduction proteins (Brink et al., 2003). For example, phosphorylation of mitogen-activated protein kinases (MAPKs) is involved in the LTB₄-induced proliferation of RAW 264.7 macrophages and bronchial SMCs (Nieves and Moreno, 2006; Watanabe et al., 2009). In addition, extracellular signal-regulated kinases (ERKs) may also be involved in LTB₄-induced proliferation, as demonstrated in vascular SMCs (Heller et al., 2005) and in signaling associated with delayed neutrophil apoptosis (Pétrin et al., 2006). The reported effects of different kinase inhibitors may also depend on which LTB₄-induced response is studied. For example, wortmannin, a phosphatidylinositol 3-kinase (PI3K) inhibitor has been reported to block LTB₄-induced chemotaxis, whereas calcium mobilization remains intact (Haribabu et al., 1999; Sabirsh et al., 2004). Tyrosine kinases have been implicated in LTB₄-signaling in neutrophil granulocytes (Dryden et al., 1992) and BLT₁-transfected HeLa cells (Sabirsh et al., 2004).

Effects on transcription have been implicated in BLT receptor intracellular signaling. For example, treatment of monocytes with LTB₄ increased the transcriptional activation of the IL-6 gene (Brach et al., 1992). In this study, a reporter gene assay identified two restricted regions within the IL-6 promoter. These binding sites for NF-IL-6 and NF- κ B conferred inducibility by LTB₄. Exogenous addition of LTB₄ increased the DNA binding of these transcription factors in monocytes (Brach et al., 1992; Huang et al., 2004) and induced nuclear translocation of NF- κ B p65 in murine bone marrow-derived dendritic cells (Toda et al., 2010). The LTB₄-induced NF- κ B DNA binding activity was abolished by the BLT₁R antagonist 1-[3-(4-phenyl-benzyl)-4-hydroxy-chroman-7-yl] cyclopentane carboxylic acid (CP-105,696) (Huang et al., 2004), suggesting that transcriptional alterations by LTB₄ may be through BLT₁R. One possible mechanism for this transcriptional activation by LTB₄ could be through LTB₄-induced intracellular H₂O₂ formation (Gagnon et al., 1989), because the oxidant scavenger *N*-acetyl-L-cysteine completely blocks LTB₄-mediated transcription factor binding in monocytes (Brach et al., 1992). However, another study failed to observe any effects of other antioxidants on IL-6 protein secretion (Rola-Pleszczynski and Stanková, 1992). In the latter study, the partial inhibition of LTB₄-induced IL-6 secretion by genistein suggested the involvement of tyrosine phosphorylation events during this process.

D. Receptor Distribution and Cellular Targets

1. Neutrophil Granulocytes. The expression of both BLT₁ and BLT₂ receptor proteins in neutrophil granulocytes has, for example, been demonstrated by immunohistochemical analysis of surgical specimens derived from human abdominal aortic aneurysms (Houard et al., 2009). The potent neutrophil chemotactic activity of LTB₄ through BLT₁R signaling has been well established (Ford-Hutchinson et al., 1980; Malmsten et al., 1980; Palmblad et al., 1981). In neutrophils derived from the synovial fluid of patients with rheumatoid arthritis, BLT₁ receptor antagonism inhibits LTB₄-induced calcium mobilization and produces a rightward shift of the peak chemotactic response. In contrast, the BLT₂R antagonist 1-[5-ethyl-2-hydroxy-4-[[6-methyl-6-(1*H*-tetrazol-5-yl)heptyl]oxy]phenyl]ethanone (LY255283) only inhibits [Ca²⁺]_i and the chemotactic response to LTB₄ at high concentrations, at which this compound may also act as an antagonist at BLT₁R (Mathis et al., 2010). Studies in knockout mouse models have also shown that the LTB₄-induced chemotaxis and calcium mobilization in zymosan-elicited murine peritoneal neutrophils derived from either WT or BLT₂ knockout mice display similar LTB₄ dose-response relations, whereas neutrophils from BLT₁R knockout and BLT₁R-BLT₂R knockout mice lack both chemotaxis and alterations of [Ca²⁺]_i in response to LTB₄ (Haribabu et al., 2000; Tager et al., 2000; Terawaki et al., 2005; Mathis et al., 2010).

In addition to chemotaxis, LTB₄ stimulates neutrophil release of lysozyme (Hafstrom et al., 1981), matrix metalloproteinases (MMP) (Kjeldsen et al., 1992), myeloperoxidase (Terawaki et al., 2005), elastase, α -defensins (Flamand et al., 2007), and azurocidin (Di Gennaro et al., 2009). Initial characterization of the binding of [³H]LTB₄ in relation to the functional effects of LTB₄ on human neutrophils suggested that whereas high-affinity binding sites mediated chemotaxis, this lysosomal degranulation occurred by LTB₄ binding to low-affinity sites (Goldman and Goetzl, 1984). Subsequent results demonstrated that both subsets of LTB₄ binding sites contributed to increases in [Ca²⁺]_i induced by LTB₄ (Goldman et al., 1985). In line with those findings, the neutrophil secretagog activity of LTB₄ has consistently been observed at higher LTB₄ concentrations compared with those needed to induce chemotaxis (Serhan et al., 1982). For example, maximal release of α -defensins from neutrophils was observed at 100 nM LTB₄ (Flamand et al., 2007), and the release of azurocidin was gradually increased at LTB₄ concentrations ranging from 10 nM to 1 μ M (Di Gennaro et al., 2009). The latter apparent low-affinity response, however, was inhibited by the selective BLT₁R antagonist CP-105,696, but not by the selective BLT₂R antagonist LY255238. Despite the low-affinity profile, further support for lysosomal enzyme release being mediated through BLT₁R rather than BLT₂R signaling has emerged from studies of knockout

mice. Although a low-affinity binding site for LTB₄ has been characterized in neutrophils derived from BLT₁R knockout mice, the myeloperoxidase release in response to LTB₄ is also abolished in those cells (Terawaki et al., 2005), hence challenging the concept of lysosomal enzyme release through BLT₂R signaling.

In addition to being a major neutrophil chemoattractant and promoting the release of lysosomal enzymes (Hafstrom et al., 1981; Serhan et al., 1982), prolonged exposure of neutrophils to LTB₄ delays their constitutive apoptosis in a time- and concentration-dependent manner (Hébert et al., 1996). Furthermore, threshold levels of LTB₄ (0.01 nM) induce surface expression of adhesion molecules, such as the β 2-integrin CD11b and Mac-1, which have been implicated in LTB₄-induced neutrophil adhesion to endothelial cells (Gimbrone et al., 1984; Showell et al., 1998). The antimicrobial neutrophil response may also be facilitated by LTB₄ through increased surface expression of Toll-like receptors 7, 8, and 9 (Gaudreault and Gosselin, 2009) and stimulated secretion of the cathelicidin LL-37 (Flamand et al., 2007; Wan et al., 2007).

2. Eosinophil Granulocytes. Western blot analysis has demonstrated BLT₁R expression in eosinophils of both murine and human origin, with up-regulated expression levels in IL-5 transgenic mice and after inhalation of mold allergen (Huang et al., 1998). Consistent with findings in neutrophils, eosinophils derived from mice (Huang et al., 1998) and guinea pigs (Ng et al., 1991; Sun et al., 1991) also display a dose-dependent bell-shaped chemotactic response to LTB₄ with an optimum concentration of 1 to 10 nM. However, species differences may exist in terms of LTB₄-induced responses in eosinophils, because human cells may be less responsive to LTB₄ when chemotaxis is monitored (Sun et al., 1991). Nevertheless, human blood-derived eosinophils and eosinophil-differentiated HL-60 cells exhibit an increase in intracellular calcium concentration upon stimulation with LTB₄ (Patry et al., 1996; Murray et al., 2003). Furthermore, in line with findings in IL-5 transgenic mice (Huang et al., 1998), human eosinophils primed with IL-5 exhibit enhanced LTB₄-induced chemotaxis (Sehmi et al., 1992). Priming with cytokines, such as IL-5, may therefore be a prerequisite for regulating the expression and responsiveness of BLT receptors on human eosinophils. In guinea pigs, LTB₄ induced eosinophil superoxide generation in vitro (Ng et al., 1991). However, in contrast to findings in neutrophils, human eosinophil apoptosis was not altered by LTB₄ (Murray et al., 2003).

There are also animal studies that support a role of LTB₄ in regulating the recruitment of eosinophils into tissues in vivo. In guinea pigs, cutaneous LTB₄ injection induces an accumulation of ¹¹¹In-marked eosinophils (Faccioli et al., 1991) and oral treatment of sensitized guinea pigs with the selective BLT₁R antagonist -[6-(3-hydroxy-1*E*,5*Z*-undecadienyl)-2-pyridinyl]-1,5-hexane-

diol (U75302) decreased eosinophil influx to the lung and BAL after antigen challenge (Richards et al., 1989). However, the studies of OVA sensitization and challenge in BLT₁R-deficient mice have generated contradictory results, with both decreased eosinophil accumulation (Terawaki et al., 2005) and no alterations compared with results in WT mice (Miyahara et al., 2005a). In support of a pathophysiological role of LTB₄-induced eosinophil activation, BLT₁R-deficient mice exhibit decreased leukocyte content in peritoneal exudates compared with those in WT mice in response to thioglycollate-induced acute peritonitis (Tager et al., 2000). Furthermore, oral treatment with the BLT₁R antagonist CP-105,696 blocked the recruitment of eosinophils into the spinal cord and completely inhibited the development of paralysis in experimental allergic encephalomyelitis (EAE), a murine model of multiple sclerosis (MS) (Gladue et al., 1996). The potential in vivo effects of either pharmacological or genetic BLT₁R targeting also reflect indirect eosinophil activation, for example, through T lymphocyte-dependent responses and Th2 cytokines, such as IL-5 and IL-13 (Miyahara et al., 2005a,b; Terawaki et al., 2005). Finally, findings that blood eosinophil counts are unaltered in BLT₁R knockout mice compared with those in WT mice have suggested that BLT₁R is not necessary for granulocytopoiesis (Terawaki et al., 2005).

3. Basophil Granulocytes. There is presently a paucity of information regarding the expression of BLT receptors on basophil granulocytes. In human blood-derived basophils, LTB₄ induces a slight chemotactic response, which is more pronounced than that observed for PAF but less than that observed with C5a (Tanimoto et al., 1992). The receptor involved in the latter response, however, is presently unknown.

4. Monocytes/Macrophages. In human blood-derived monocytes, LTB₄ induces a dose-dependent increase in $[Ca^{2+}]_i$ with an ED₅₀ of approximately 1.0 nM, which is inhibited by PTX (Rediske et al., 1993). Furthermore, BLT₁R protein has been demonstrated on human blood-derived monocytes by fluorescence-activated cell sorting (Friedrich et al., 2003; Pettersson et al., 2003). An analysis of monocyte subpopulations suggested that BLT₁R protein is more abundantly expressed in monocytes with high CD14 expression compared with CD16⁺ monocytes (Pettersson et al., 2005).

In addition to chemotaxis, BLT₁R signaling in human monocytes also induced an up-regulation of integrin expression, involved in monocyte adhesion to endothelial cells in vitro and in vivo (Vaddi and Newton, 1994; Friedrich et al., 2003). Furthermore, LTB₄-induced activation of human monocytes has been associated with the release of IL-1 β (Rola-Pleszczynski and Lemaire, 1985), IL-6 (Brach et al., 1992; Rola-Pleszczynski and Stanková, 1992), and monocyte chemoattractant protein 1 (MCP-1) (Huang et al., 2004).

BLT₁R expression has also been demonstrated on peritoneal and alveolar macrophages and in RAW 264.7

cells (Huang et al., 1998; Toda et al., 1999). In the latter macrophage cell line, LTB₄ induces increased proliferation and [³H]thymidine uptake, suggesting that LTB₄ may also have mitogenic effects on macrophages (Nieves and Moreno, 2006).

Early studies had shown that LTB₄ enhanced macrophage bacterial phagocytosis in vitro (Demitsu et al., 1989). Subsequent results have demonstrated that this effect required the cells to be opsonized with IgG and that LTB₄ enhanced only Fc receptor (FcR)-mediated phagocytosis (Mancuso and Peters-Golden, 2000), whereas the phagocytosis of apoptotic cells (efferocytosis) was not affected by LTB₄ (Canetti et al., 2003). The signaling pathways involved in LTB₄-enhanced FcR-dependent phagocytosis include G α_{i3} protein (Peres et al., 2007), PKC activation (Mancuso and Peters-Golden, 2000), and the tyrosine kinase Syk (Canetti et al., 2003). It is noteworthy that a recent report demonstrated that FcR engagement results in tyrosine phosphorylation of BLT₁R by the Src family of kinases, which leads to a molecular complex within plasma membrane lipid rafts comprising the FcR, BLT₁R, G α_{i3} protein, and Src (Serezani et al., 2009). Because disruption of lipid rafts abolished the LTB₄-enhanced phagocytosis in the latter study, the formation of a complex between BLT₁R and immunoreceptors may represent a major mechanism in macrophage phagocytosis.

Several of the LTB₄-induced responses in monocytes/macrophages, such as MCP-1 secretion, integrin-dependent monocyte arrest, and macrophage phagocytosis enhancement, are blocked by selective BLT₁R antagonists (Friedrich et al., 2003; Huang et al., 2004). However, BLT₂ receptor mRNA has also been detected in human monocytes (Yokomizo et al., 2001a). Furthermore, BLT₁ and BLT₂ receptor expression has been demonstrated immunohistochemically in macrophage-rich areas within human atherosclerotic lesions (Bäck et al., 2005) and abdominal aortic aneurysms (Houard et al., 2009), as well as by in situ hybridization of macrophages in synovial tissues from patients with rheumatoid arthritis (Hashimoto et al., 2003). Although an initial study demonstrated that macrophages derived from BLT₁R knockout mice did not alter $[Ca]_i$ after LTB₄ stimulation (Tager et al., 2003), a subsequent study reported that these cells display chemotaxis toward LTB₄ albeit at 100-fold higher concentrations than that in WT macrophages (Subbarao et al., 2004). The latter observation suggests that the low-affinity BLT₂ receptor may be involved in LTB₄-induced monocyte/macrophage chemotaxis. Based on results obtained in transfected CHO cells, in which expression of one BLT receptor leads to chemotaxis toward a narrow range of LTB₄ concentrations, coexpression of human BLT₁ and BLT₂ receptors makes cells migrate toward a wider range of LTB₄ concentrations (Yokomizo et al., 2001a).

5. Dendritic Cells. Dendritic cells (DCs) are antigen-presenting cells that control adaptive immunity through

direct interaction with T lymphocytes. Initially, human monocyte-derived DCs were reported to express mRNA for BLT₂R but not BLT₁R and the LTB₄-induced DC chemotaxis was reported to be inhibited by the BLT₂R antagonist LY255283 (Shin et al., 2006). However, a subsequent study revealed BLT₁R protein expression by flow cytometric analysis of human DCs (Toda et al., 2010). The latter finding was in line with the demonstration of BLT₁R but not BLT₂R mRNA in murine bone marrow-derived DCs (BMDCs) (Toda et al., 2010). The latter cells exhibit functional responses to LTB₄, such as increased $[Ca^{2+}]_i$ and chemotaxis (Del Prete et al., 2007; Toda et al., 2010), not observed in BMDCs derived from either BLT₁R or BLT₁R and BLT₂R knockout mice (Del Prete et al., 2007; Toda et al., 2010). Other responses associated with LTB₄ stimulation of murine DCs include induction of the chemokine receptor CCR7 (Del Prete et al., 2007), IL-12 secretion, and NF- κ B translocation (Toda et al., 2010). Furthermore, murine DCs lacking both BLT₁R and BLT₂R exhibited decreased *in vivo* migration to draining lymph nodes after either paw injection (Del Prete et al., 2007) or intratracheal instillation (Miyahara et al., 2008). *In vivo* models have also implicated a pathophysiological role for DC BLT receptors by demonstrating decreased airway hyperreactivity after transfer of OVA-pulsed BLT₁R-deficient BMDCs compared with wild-type BMDCs (Miyahara et al., 2008) and decreased skin contact hypersensitivity in BLT₁R and BLT₂R knockout mice (Del Prete et al., 2007). Finally, the OVA-dependent cytokine production in mouse splenocytes after adoptive transfer of BLT₁R-deficient BMDCs exhibited decreased production of the Th1 cytokine IFN- γ and elevated levels of the Th2 cytokines IL-4 and IL-5 (Toda et al., 2010).

6. T Lymphocytes. The chemotactic response of human blood-derived human T lymphocytes was initially reported to exhibit a peak concentration of LTB₄ at 10^{-8} M (i.e., a lower potency compared with granulocytes) (Leppert et al., 1995). The latter observation was supported by the binding of radioactive LTB₄ to the CD4⁺8⁺3^{low} Tsup-1 cell line, which was characterized by a K_d of approximately 200 nM and a rank order of competitive potencies of 20-OH-LTB₄, 6-*trans*-LTB₄, which were both similar to that of the low-affinity subset of human neutrophil LTB₄-binding sites (Leppert et al., 1995). Subsequent studies of peripheral blood cells have supported those initial observations by the identification of dominant levels of BLT₂R mRNA compared with BLT₁R mRNA (Yokomizo et al., 2001a). Moreover, in peripheral blood, LTB₄ bound only to 11% of T lymphocytes, representing mainly cells of the CD8⁺ subset (Payan et al., 1984). The latter observation was subsequently supported by a flow cytometric demonstration of BLT₁ and CD8 coexpression in a small fraction of peripheral blood cells, whereas CD4⁺ lymphocytes were BLT₁R-negative (Pettersson et al., 2003). However, decreased BLT₂R expression has been observed after T-

lymphocyte stimulation (Yokomizo et al., 2001a), and animal studies indicate that BLT₁R activation may be the major signaling pathway mediating LTB₄-induced T lymphocyte recruitment *in vivo* (Goodarzi et al., 2003; Tager et al., 2003; Miyahara et al., 2005a). Furthermore, morphological analyses have associated adventitial vascular inflammation with an accumulation of BLT₁R-expressing T lymphocytes (Houard et al., 2009).

BLT₁R mRNA expression is induced in antigen-exposed murine CD8⁺ T-effector cells, associated with an increased chemotactic response; effects inhibited either by the BLT₁R antagonist CP-105,696 or in cells derived from BLT₁R knockout mice (Goodarzi et al., 2003; Ott et al., 2003). These findings suggest that the ability to use BLT₁R for migration into inflamed tissues is a feature specific to fully differentiated CD8⁺ effector cells (Goodarzi et al., 2003). Likewise, BLT₁R mRNA is induced in CD4⁺ murine lymphocytes during either Th1 or Th2 polarization (Tager et al., 2003). A subsequent study of human blood-derived T lymphocytes demonstrated that the small fraction of BLT₁R-positive cells also were enriched for the activation markers CD38 and HLA-DR and expressed the effector cytokines IFN- γ and IL-4 (Islam et al., 2006). Furthermore, *in vitro* activation of human T lymphocytes by alloactivated DCs increased BLT₁R surface expression and enhanced LTB₄-induced chemotaxis (Islam et al., 2006). In further support of an up-regulation of BLT₁R in activated T lymphocytes, the number of circulating CD8⁺ cells positive for BLT₁R was increased during acute Epstein-Barr virus infection (Islam et al., 2006). Finally, bronchoalveolar lavage derived from patients with lung transplant graft dysfunction (Medoff et al., 2005) and asthma (Islam et al., 2006) contained an increased proportion of BLT₁R-positive T lymphocytes.

LTB₄ stimulation also enhanced the production of IL-1, IL-2, IL-5, and IFN- γ in human blood-derived T lymphocytes *in vitro* (Rola-Pleszczynski et al., 1986; Yamaoka and Kolb, 1993) and the production of MMP-2, -3, and -9 in CD4⁺8⁺3^{low} Tsup-1 cells (Leppert et al., 1995). Furthermore, LTB₄ inhibited the differentiation of murine naive CD4⁺ T lymphocytes into CD25⁺ Foxp3⁺ T regulatory cells and increased IL-17 expression (Chen et al., 2009a), providing the first suggestion that LTB₄ may counteract the generation of immunosuppressive T regulatory cells and promote the differentiation into Th17 cells. In support of a role for LTB₄ in the development of Th17 immune responses, lymph node cells derived from BLT₁R knockout mice after EAE induction exhibit decreased IL-17 production (Kihara et al., 2010).

The role of BLTR signaling in T lymphocyte recruitment has also received support from *in vivo* studies. The pulmonary inflammation and airway hyperresponsiveness after OVA sensitization and challenge are reduced in BLT₁R knockout mice and restored after reconstitution with BLT₁R-expressing T lymphocytes (Tager et al.,

2003; Miyahara et al., 2005a). In addition, mice lacking CD8⁺ T lymphocytes are protected from airway hyper-responsiveness induced by allergen sensitization and challenge (Miyahara et al., 2005b). Whereas reinstallation of CD8⁺ cells restored airway hyperresponsiveness in the latter mice, adoptive transfer of BLT₁R-deficient CD8⁺ cells maintained the protective effect (Miyahara et al., 2005b). In other models, such as complete Freund's adjuvant-induced peritonitis, adoptive transfer of fluorescence-marked T lymphocytes derived from both BLT₁R-deficient and WT mice resulted in an accumulation of 1.6- to 1.9-fold higher numbers of WT cells in peritoneal exudates (Goodarzi et al., 2003).

7. B Lymphocytes. BLT₁R protein and BLT₁R and BLT₂R mRNA have been detected in CD19⁺ human B lymphocytes (Yokomizo et al., 2001a; Pettersson et al., 2003; Runarsson et al., 2005). In cells derived from either blood or tonsillectomy tissues, LTB₄ enhances the effects of other stimulating factors on CD23 expression, proliferation, and differentiation of resting, but not activated, B lymphocytes (Yamaoka et al., 1989, 1994; Dugas et al., 1990). The latter findings were subsequently supported by the demonstration that Epstein-Barr virus infection of B lymphocytes is associated with a loss of BLT₁R expression and a lack of LTB₄-induced effects on the proliferation of infected cells (Liu et al., 2008). BLT₁R protein expression has also been demonstrated in B lymphocytes derived from patients with B-cell chronic lymphocytic leukemia (Runarsson et al., 2005). In this study, LT synthesis inhibitors decreased DNA synthesis and antigen expression in B-cell chronic lymphocytic leukemia lymphocytes, an effect that was reversed by exogenously added LTB₄ (Runarsson et al., 2005).

8. Mast Cells. Experiments in human umbilical cord blood-derived mast cells have demonstrated that LTB₄ is a chemoattractant for the immature c-kit⁺ MC populations, whereas the mature c-kit^{high} MCs are unresponsive (Weller et al., 2005). The chemotactic effects induced by LTB₄ on murine bone marrow-derived mast cells (BMMCs) cultured in the presence of IL-3 may also depend on the maturity of the MC, because cells cultured for 2 to 6 weeks migrate in response to LTB₄ (Kitaura et al., 2005; Weller et al., 2005; Lundeen et al., 2006), whereas after 10 weeks of culture, the cells are unresponsive to this agonist (Weller et al., 2005). The latter finding correlated with a decrease in BLT₁R mRNA. For example, 2-week-old BMMCs expressed 4-fold higher levels than 6-week-old cells and 10-fold more than 10-week-old cells (Weller et al., 2005). A subsequent study also described BLT₂R mRNA in BMMC after 4 weeks of culture and indicated that either the BLT₁R antagonist U75302 or the BLT₂ receptor antagonist LY255283 inhibited LTB₄-induced BMMC chemotaxis, although no additive effect was observed after combination of the two receptor antagonists (Lundeen et al., 2006). In addition, antigen stimulation in-

creased BLT₂R expression in murine BMMCs (Cho et al., 2010a). In support of a functional murine MC BLT₂ receptor, the BLT₂ receptor agonists 12-HHT and 12(S)-HETE have also been reported to induce BMMC migration (Lundeen et al., 2006; Okuno et al., 2008). The [Ca²⁺]_i induced by 12-HHT was abolished in BMMCs derived from BLT₂R knockout mice, whereas BMMCs from both WT and BLT₁R knockout mice responded to LTB₄ (Mathis et al., 2010). However, LTB₄-induced migration was abolished in BMMCs derived from BLT₁R-deficient mice, whereas 12-HHT-induced migration was abolished in BMMCs derived from BLT₂R-deficient mice (Okuno et al., 2008). Finally, a human MC line, HMC-1, has been reported to express both BLT₁ and BLT₂ receptor mRNA and migrate in response to LTB₄ (Lundeen et al., 2006). An unexpected finding was that flow cytometry and immunostaining suggested an intracellular localization of BLT₁R protein in these cells (Lundeen et al., 2006), but the functional significance of this receptor localization remains to be established.

9. Vascular Smooth Muscle Cells. The LTB₄-induced vasoconstriction, demonstrated in human pulmonary artery (Sakata et al., 2004), in guinea pig pulmonary artery and aorta (Bäck et al., 2004; Sakata et al., 2004), and in rat basilar artery (Trandafir et al., 2005), has led to the hypothesis that nonmyeloid cells, such as SMCs, also express BLT receptors. Immunohistochemical analysis of human arteries has revealed BLT₁R expression in the muscular layers of carotid atherosclerotic endarterectomies, as well as in human nonatherosclerotic mammary arteries (Bäck et al., 2005). Moreover, in human coronary artery SMCs, 8-fold higher BLT₁R mRNA levels compared with BLT₂R mRNA has been demonstrated by RT-PCR (Heller et al., 2005), supporting the observation that the BLT₁R subtype may be the dominant BLT receptor subtype in vascular SMCs. The expression of BLT₁R proteins on human coronary artery SMCs has also been demonstrated by Western blot (Bäck et al., 2005) and flow cytometry (Heller et al., 2005). In contrast to this apparent constitutive BLT₁R expression in human coronary artery SMCs, murine aortic SMCs express BLT₁R mRNA only after 24 h of treatment with TNF-α and IFN-γ (Heller et al., 2005).

In human coronary artery SMCs, LTB₄ induced an approximately 4-fold increase in whole-cell currents measured by patch clamp, and the activation of SMC by LTB₄ induces migration and proliferation (Bäck et al., 2005). Furthermore, LTB₄ stimulated the release of MMP-2 (Hlawaty et al., 2009; Seo et al., 2010) and activation of integrin signaling pathways in vascular SMCs (Moraes et al., 2010). The pathophysiological importance of LTB₄-induced activation of SMCs in the context of atherosclerosis has been reinforced by the inhibitory effects of BLT receptor antagonists on the development of intimal hyperplasia after vascular injury (Kondo et al., 1998; Bäck et al., 2005; Hlawaty et al., 2009). Furthermore, atherosclerotic lesions of apoE(−/−) mice

display reduced SMC content after BLT₁R gene disruption (Heller et al., 2005).

10. Bronchial Smooth Muscle Cells. In line with findings in human vessels, immunohistochemical staining of human bronchi revealed colocalization of both BLT₁R and BLT₂R protein with smooth muscle α -actin-positive airway SMCs (Watanabe et al., 2009). Furthermore, both receptors were also identified on human airway SMCs in culture by RT-PCR, Western blot analysis, and flow cytometry. In the latter cells, LTB₄ induced proliferation and migration, which was inhibited by the selective BLT₁R antagonist U75302 (Watanabe et al., 2009).

11. Endothelial Cells. In human vessels, endothelial expression of BLT₁R has been demonstrated by immunohistochemical analysis and was only observed in atherosclerotic and not in healthy arteries, suggesting an induction during vascular inflammation (Bäck et al., 2005). The latter notion of BLT₁R immunoregulation has received support from studies in HUVECs demonstrating BLT₁R up-regulation by LPS and IL-1 β (Table 2), whereas BLT₂R was induced by TNF- α (Qiu et al., 2006).

LTB₄-induced endothelial activation has also been implicated in increased leukocyte adherence (Hoover et al., 1984). However, the in vitro neutrophil adherence observed after LTB₄ stimulation of HUVECs is weak (Lindström et al., 1990; Palmblad et al., 1994), and the role of endothelial BLT receptors in leukocyte adhesion is today not fully characterized. Papayianni et al. (1996) demonstrated that LTB₄ had no effect on P-selectin expression in HUVECs. Another study reported no effect on monocyte arrest under physiological flow conditions after EC stimulation with LTB₄ (Friedrich et al., 2003). These observations provided evidence for a direct effect of LTB₄ on leukocytes rather than on ECs. However, other investigators demonstrated that the endothelium released vasoactive factors via BLT receptor activation (Bäck et al., 2004; Qiu et al., 2006). These reports provide evidence for a role of LTB₄ in regulating endothelial function. In addition, vascular endothelial growth factor (VEGF) up-regulated the expression of BLT₁R and BLT₂R mRNA and protein in HUVECs (Kim et al., 2009). It is noteworthy that VEGF also increased the release of 12(S)-HETE, and the VEGF-induced blood

vessel formation in vivo and in vitro was inhibited by either the BLT₂R antagonist LY255283 or BLT₂R knock down by small interfering RNA (Kim et al., 2009). These findings suggest a role for 12(S)-HETE signaling through endothelial BLT₂R in angiogenesis. Taken together, the data indicate that the ligands for the BLT receptors affect ECs but that the interaction between the ligands and the endothelium in adhesion experiments is presently difficult to observe, possibly being masked by the LTB₄-induced effects on leukocytes.

E. BLT Receptor Functional Analysis through Altered Gene Expression

1. BLT Receptor Transgenic Models. Transgenic mice expressing the human BLT₁R under the CD11b promoter to obtain leukocyte specific expression exhibit an increased granulocyte infiltration in response to topical LTB₄ application and ischemia reperfusion (Chiang et al., 1999; Brink et al., 2003). In addition, transgenic BLT₂R overexpressed in mice have been studied in a model of angiogenesis and shown to exhibit increased blood vessel formation in response to LTB₄ and 12(S)-HETE (Kim et al., 2009).

2. BLT₁ Receptor Knockout. Mice lacking BLT₁R were generated in 2000 (Haribabu et al., 2000; Tager et al., 2000; Brink et al., 2003). Although these mice developed normally and had no apparent hematopoietic abnormalities, decreased leukocyte chemotaxis (Haribabu et al., 2000; Tager et al., 2003) and integrin-mediated leukocyte arrest in postcapillary venules (Tager et al., 2003) in response to LTB₄ compared with WT mice were reported. In addition, BLT₁R deficiency conferred protection against inflammatory responses in different disease models.

After induction of acute peritonitis, BLT₁R-deficient mice exhibit decreased leukocyte content in peritoneal exudates compared with that in WT mice (Haribabu et al., 2000; Tager et al., 2000; Goodarzi et al., 2003). Other in vivo studies of endotoxin provocation have demonstrated decreased portal venule leukocyte adherence in response to systemic LPS in BLT₁R knockout mice compared with that in WT mice (Ito et al., 2008), whereas the leukocyte infiltration after local intraocular LPS injection was not altered by BLT₁R disruption (Smith et

TABLE 2
Immunoregulation of human BLT₁R expression

Receptor	Cytokine	Cell	Effect ^a	Reference
BLT ₁	IFN- γ TNF- α	Monocytes	↓ mRNA; ↓ protein; ↓ chemotaxis	Pettersson et al., 2005
		Monocytes	↓ mRNA; ↓ protein	Pettersson et al., 2005
		Granulocytes	↓ protein	Pettersson et al., 2003
	IL-1 β	Vascular SMCs	↑ mRNA	Bäck et al., 2005
		HUVECs	↑ mRNA; ↑ protein	Qiu et al., 2006
	IL-10	Monocytes	↑ mRNA; ↑ protein	Pettersson et al., 2005
		Monocytes	↓ mRNA	Pettersson et al., 2005
	LPS	Granulocytes	↓ protein	Pettersson et al., 2003
		Vascular SMCs	↑ mRNA	Bäck et al., 2005
		HUVECs	↑ mRNA; ↑ protein; ↑ [Ca ²⁺] _i	Qiu et al., 2006
	IL-5	Eosinophils	↑ chemotaxis	Sehmi et al., 1992; Thivierge et al., 2000

^a ↑, up-regulation; ↓, down-regulation; specified are the effects (at mRNA, protein, and functional level).

al., 2004). In addition to models of acute inflammation, BLT₁R knockout mice have also revealed decreased inflammation in more chronic inflammatory responses. For example, in contrast to the lack of effects on endotoxin-induced uveitis, BLT₁R-deficient mice were protected from experimental autoimmune uveitis induced by immunization of interphotoreceptor retinoid-binding protein (Liao et al., 2006).

Mice lacking apolipoprotein E exhibit hyperlipidemia and develop spontaneous atherosclerosis. Apolipoprotein E and BLT₁R double knockout mice display smaller lesions compared with their apoE(−/−) littermates (Subbarao et al., 2004; Heller et al., 2005; Bäck, 2008b). The latter double knockout mice are also protected from abdominal aortic aneurysm development induced by angiotensin II infusion (Ahluwalia et al., 2007).

After OVA sensitization, BLT₁R knockout mice exhibit decreased airway responsiveness associated with a decreased leukocyte accumulation (Tager et al., 2003; Miyahara et al., 2005a; Terawaki et al., 2005), which is restored after adoptive transfer of BLT₁R-expressing T lymphocytes (Miyahara et al., 2005a; Tager et al., 2003) (see section II.D). In the EAE model, BLT₁R-deficient mice develop less severe clinical signs of disease and a significantly delayed onset of disease than WT mice, associated with decreased inflammatory infiltration in the spinal cord (Kihara et al., 2010). Finally, BLT₁R knockout mice are protected in models of both collagen- and K/BxN serum-induced arthritis (Kim et al., 2006a; Shao et al., 2006; Mathis et al., 2010), discussed in detail below. In this context, BLT₁R knockout mice displayed a decrease in bone resorption induced by either LPS or ovariectomy (Hikiji et al., 2009).

3. BLT₂ Receptor Knockout. In recent studies, BLT₂R knockout mice were generated (Iizuka et al., 2010; Mathis et al., 2010). Because of the close proximity of the BLT₁R gene promoter, the BLT₂R gene disruption was generated through insertion into the open reading frame of the BLT₂ gene to avoid alterations of BLT₁R expression (Iizuka et al., 2010; Mathis et al., 2010). The BLT₂R-deficient mice were viable, developed normally, and displayed no overt behavioral or morphological defects (Mathis et al., 2010). An unexpected finding was that opposing phenotypic changes were observed in two different mouse models of disease. BLT₂R knockout mice displayed attenuated inflammatory arthritis in response to K/BxN serum transfer (Mathis et al., 2010). The latter effect was associated with decreased inflammatory cell influx and could be reproduced by bone marrow transplantation, suggesting that leukocyte BLT₂R is necessary for full arthritis development (Mathis et al., 2010). However, the protection against K/BxN serum-induced arthritis conferred by the lack of BLT₁R is more pronounced compared with that observed in BLT₂R-deficient mice (Kim et al., 2006a; Mathis et al., 2010). Nevertheless, the transfer of WT neutrophils into BLT₁R knockout mice promoted the

entry of endogenous BLT₁R-deficient neutrophils into the joints of these mice (Kim et al., 2006a) through the production of IL-1 (Chou et al., 2010). Taken together, these data suggested that although the BLT₁R may be necessary for the initiation of autoantibody-induced arthritis, BLT₂R may play a possible role at later stages of disease, when local LTB₄ concentrations are higher in the joint (Mathis et al., 2010). In contrast to the findings of decreased arthritis in BLT₂R knockout mice, another study demonstrated that this gene disruption induced more severe colitis in response to dextran sodium sulfate (DSS) compared with that in either WT or BLT₁R knockout mice, which was accompanied by increased expression of inflammatory cytokines, chemokines, and MMPs (Iizuka et al., 2010). However, in the latter study, BLT₂R deficiency was associated with a dysfunctional barrier function in colonic epithelial cells rather than direct effects on leukocytes (Iizuka et al., 2010). Although the effects of DSS-induced colitis have not been fully explored in BLT₁R knockout mice, those mice exhibit weight loss similar to that in WT mice, suggesting no protective effects. The notion that BLT₂R agonists other than LTB₄ may be involved in the exacerbated colitis observed after BLT₂R knockout (Iizuka et al., 2010) is supported by the fact that HHT is produced at 5- to 6-fold higher levels compared with LTB₄ in inflamed colonic biopsy specimens (Zijlstra et al., 1992, 1993) (see section II.E).

4. BLT₁ and BLT₂ Receptor Double Knockout. Double knockout of BLT₁R and BLT₂R has been generated through direct targeting of the genes encoding both receptors (Shao et al., 2006). In line with findings after disruption of any of the BLT receptor subtypes alone (see above), these mice were also viable, developed normally, and displayed no overt behavioral or morphological defects and no alterations of leukocyte subpopulation counts (Shao et al., 2006). After collagen-induced arthritis, both BLT₁R knockout and BLT₁R-BLT₂R knockout mice respond in a similar fashion with less clinical and histological signs of arthritis, as well as smaller synovial inflammatory cell infiltration compared with WT mice, without altering the antibody response (Shao et al., 2006).

F. Potential Therapeutic Applications

The cell-type specific BLTR signaling discussed above (see section II.D) may imply differential effects of LTB₄ in the development of different diseases. For example, LTB₄ may mainly exert its effects on neutrophil granulocytes in models of arthritis (Kim et al., 2006a) abdominal aortic aneurysms (Houard et al., 2009), and cerebral ischemia/reperfusion (Barone et al., 1992), whereas models of MS have implicated a major role of LTB₄-induced effects on eosinophil granulocytes (Gladue et al., 1996). In contrast, T lymphocytes may be the main effector cells in LTB₄-induced airway hyperresponsiveness (Miyahara et al., 2005a). Furthermore, in other

disease models, LTB₄ signaling may affect several cell types, such as in atherosclerosis, in which macrophages, vascular SMCs, and ECs express BLT₁ receptors (Bäck et al., 2005). The roles of LTs and related lipid mediators in various diseases have been extensively reviewed (Shimizu, 2009).

1. Atherosclerosis. The uptake and modification of lipids in the vascular wall induce a local inflammatory reaction, eventually developing into an atherosclerotic lesion. Generation of LTB₄ has been described in ex vivo stimulated atherosclerotic vessels, and intraluminal LT formation has been demonstrated during coronary balloon angioplasty (Brezinski et al., 1992; Bäck, 2008b). In addition, several of the BLT receptor-expressing immune cells discussed above are present in the atherosclerotic lesion (Bäck, 2008b). Although studies of targeted 5-LO have generated contradictory results, BLT₁R knock out (Subbarao et al., 2004; Heller et al., 2005) and the BLT₁R antagonist CP-105,696 (Aiello et al., 2002) reduces atherosclerosis in hyperlipidemic mice (Bäck, 2008b). In addition to effects on the inflammatory response, LTB₄ signaling through BLT₁R expressed in vascular SMCs may also be involved in the development of atherosclerosis and intimal hyperplasia after vascular interventions (Bäck et al., 2005; Heller et al., 2005; Hlawaty et al., 2009). Clinical trials have been initiated to evaluate the effects of anti-LTs on biomarkers and atherosclerosis morphology in patients with coronary heart disease (Bäck, 2009a).

2. Aortic Abdominal Aneurysms. Circulating neutrophils derived from patients undergoing surgery for abdominal aortic aneurysms produce increased levels of LTB₄ (Gadaleta et al., 1994), and the expression levels of LTB₄ synthesizing enzymes has in addition been demonstrated in neutrophils infiltrating the intraluminal thrombus covering the aneurysm (Houard et al., 2009). This local LTB₄ production has also been demonstrated to transduce the major part of the chemotactic activity derived from the intraluminal thrombus (Houard et al., 2009). In addition to neutrophils, BLTR-positive macrophages and T lymphocytes may be involved in the adventitial inflammation, which is part of the pathogenesis of abdominal aortic aneurysms (Houard et al., 2009). The importance of BLT₁R signaling has also received support from animal studies. Either genetic or pharmacological targeting of BLT₁R signaling reduces the incidence of experimental abdominal aortic aneurysms induced by angiotensin infusion in apoE knockout mice (Ahluwalia et al., 2007; Kristo et al., 2010).

3. Cerebrovascular Disease. Leukotrienes are produced during cerebral ischemia, and LT synthesis inhibitors limit the damage after experimental cerebral ischemia and reperfusion (Bäck, 2009b). Although most studies on the receptors involved in this protective effect have focused on CysLTRs and more recently GPR17 (see section III.H), there are also studies supporting a role for BLTR signaling in cerebrovascular disease. In a study in

rats, temporary middle cerebral artery occlusion followed by reperfusion time dependently increased LTB₄ binding in the cerebral cortex, which was paralleled by increases in myeloperoxidase activity (Barone et al., 1992). The results of the latter study suggested increased LTB₄ binding to receptors located on accumulating neutrophils in ischemic brain tissue (Barone et al., 1992).

In human cerebrovascular disease, macrophage 5-LO expression and LTB₄ production have been reported to correlate with either clinical or radiological signs of cerebral ischemia in patients undergoing vascular surgery for carotid artery stenosis (Cipollone et al., 2005). Furthermore, BLT₁R and BLT₂R are expressed within carotid artery atherosclerotic lesions (Bäck et al., 2005). Finally, and as stated above (see section II.A), haplotypes within the *LTB4R* and *LTB4R2* gene complex conferred a 2.3-fold increased risk for ischemic stroke in two case-control studies (Bevan et al., 2008).

4. Multiple Sclerosis. MS is an inflammatory disorder of the central nervous system associated with blood-brain barrier breakdown, inflammatory cell accumulation, and myelin degradation (Mirshafiey and Jadidi-Niaragh, 2010). As discussed above (see section II.D), the beneficial effects on EAE after either genetic or pharmacological BLT₁R targeting (Fretland et al., 1991; Gladue et al., 1996; Kihara et al., 2010) suggest that BLT₁R signaling may potentially affect both the onset and severity of MS. In support of this, increased levels of LTB₄ have been detected in cerebrospinal fluid from patients with MS (Neu et al., 1992, 2002). Of interest, 5-LO was identified as one of the most up-regulated genes by microarray analysis in both human MS lesions and in brains from mice after EAE induction (Whitney et al., 2001). In the brain parenchyma around MS lesions, 5-LO expression colocalized with macrophages (Whitney et al., 2001). However, in contrast to findings in BLT₁R knockout mice (Kihara et al., 2010), 5-LO-deficient mice exhibit an exacerbated EAE compared with WT mice (Emerson and LeVine, 2004). These opposing effects of targeting either LT synthesis or LT receptors are in line with findings in atherosclerosis (see above) and point to the fact that targeting 5-LO will inhibit both proinflammatory mediators (i.e., LTs) and anti-inflammatory mediators (i.e., lipoxins), as has been demonstrated in 5-LO-deficient mice (Bafica et al., 2005). This, in turn, suggests that endogenous anti-inflammatory mediators derived from 5-LO metabolism may be involved in regulating these disease models. In addition, studies in mice lacking 12/15-LO have also shown exacerbated EAE (Emerson and LeVine, 2004) or a defect in both corneal reepithelization and neutrophil recruitment that correlates with a reduction in endogenous lipoxin formation (Gronert et al., 2005), raising the notion that lipoxins, for which the biosynthesis involves both 5-LO and 12/15-LO (Serhan et al., 2008), may be beneficial in MS. These findings suggest that BLT receptor antago-

nism may represent an advantage compared with 5-LO inhibition in MS.

5. Arthritis. BLTR expression has been demonstrated in synovial tissues derived from patients with rheumatoid arthritis (Hashimoto et al., 2003). The beneficial effects in models of rheumatoid arthritis after genetic disruption of BLT₁R and/or BLT₂R in C57BL/6 mice (Kim et al., 2006a; Shao et al., 2006; Mathis et al., 2010) were discussed above (see section II.E. Pharmacological treatment with the BLT₁R antagonist CP-105,696 reduced the histological signs of collagen-induced arthritis in the more arthritis-prone DBA/1J mice (Griffiths et al., 1995). In humans, oral administration of the BLT receptor antagonist amebulant (Birke et al., 2001) inhibits Mac-1 expression on neutrophils (Alten et al., 2004), but clinical trials in patients with arthritis have not shown any statistically significant beneficial effects (Díaz-González et al., 2007).

6. Pulmonary Inflammation. Although most studies of LTs in asthma have focused on CysLT receptor signaling (see section III.A), several studies point to a participation of LTB₄ in chronic airway inflammation. For example, whereas CysLT₁R antagonists generally have small effects on the increased bronchial responsiveness in asthma, clinical trials of either 5-LO inhibitors or FLAP antagonists have been more effective, supporting an involvement of LTB₄ (Dahlén, 2006). In addition, neutrophil recruitment to the airway is thought to be a major component of continuing inflammation and progression of chronic obstructive pulmonary disease (COPD), and the 46% of the neutrophil chemotactic activity in sputum derived from patients with COPD is inhibited by a BLT receptor antagonist (Woolhouse et al., 2002). Increased concentrations of LTB₄ have also been reported in BAL (Wenzel et al., 1995) and exhaled breath condensates from patients with asthma (Csoma et al., 2002). In further support of a role of BLT₁R signaling in asthma, the BLT₁R antagonist CP-105,696 decreased airway hyperresponsiveness in a primate model of asthma (Turner et al., 1996). As discussed above (section II.E), BLT₁R knockout mice exhibited decreased airway responsiveness after OVA sensitization and challenge, associated with decreased pulmonary inflammation and mucus secretion compared with that in WT mice (Miyahara et al., 2005a; Terawaki et al., 2005). In addition, BLT₂R signaling may be involved in the response to OVA sensitization and challenge, as suggested by the reduced airway inflammation and reduced airway hyperresponsiveness after BLT₂R targeting through in vivo administration of either the BLT₂R antagonist LY255283 or an antisense BLT₂R (Cho et al., 2010b).

In a crossover study of 12 atopic asthmatic individuals, the BLT receptor antagonist LY293111, 2-[2-propyl-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]propoxy]phenoxy]benzoic acid (LY293111) did not alter

either lung function or airway reactivity after allergen challenge but significantly reduced the number of neutrophils in BAL derived from treated patients compared with placebo (Evans et al., 1996).

7. Inflammatory Bowel Disease. Colonic mucosa derived from patients with inflammatory bowel disease (IBD) exhibit increased mRNA levels of LT-forming enzymes and enhanced LTB₄ production (Sharon and Stenson, 1984; Jupp et al., 2007). However, studies performed with ex vivo stimulated human colonic mucosa have revealed that lower amounts of LTB₄ are released compared with other arachidonic acid metabolites (Zijlstra et al., 1992, 1993). For example, 15-HETE is the dominant product formed after addition of exogenous arachidonic acid to human biopsy specimens obtained at colonoscopy (Zijlstra et al., 1992, 1993). Furthermore, HHT, which may act as a high-affinity BLT₂R ligand (see section II.A and Fig. 1), is produced at 5- to 6-fold higher concentration compared with LTB₄ (Zijlstra et al., 1992, 1993). Nevertheless, the exact role of these ligands and the two BLTR subtypes in IBD remains to be established. Whereas different BLTR antagonists inhibit colonic inflammation and neutrophil infiltration in animal models of IBD (Fretland et al., 1990, 1991), BLT₂R-deficient mice exhibit exacerbated colonic inflammation (Iizuka et al., 2010).

8. Cancer. LTB₄ levels are increased in different human cancer tissues, such as prostate (Larré et al., 2008) and oral (el-Hakim et al., 1990) cancers. Furthermore, immunohistochemical analysis has revealed expression of BLT receptors in human pancreatic and colon cancers (Hennig et al., 2002; Ihara et al., 2007). As outlined above, LTB₄ signals through pathways associated with cell proliferation, such as MAPK, ERK, and PI3K, which has also been implicated in tumor growth (Tong et al., 2005; Ihara et al., 2007). In support of the latter suggestion, in vitro studies have shown that LTB₄ promotes and that BLT₁R antagonists inhibit the proliferation of cultured human cancer cell lines (Earashi et al., 1995; Bortuzzo et al., 1996; Ihara et al., 2007). In addition to direct effects on tumor cells, the BLT₂ receptor-associated angiogenesis discussed above (see section II.A) (Kim et al., 2009) may potentially also be involved in LTB₄-induced cancer growth (Wang and Dubois, 2010a).

Administration of the BLT₁R antagonist LY293111 after transplantation of human cancer cells to athymic mice resulted in reduced tumor growth and reduced incidence of metastases (Hennig et al., 2004, 2005). However, results from clinical trials using the latter antagonist in combination with gemcitabine did not improve the prognosis for patients with either pancreatic or lung cancer (Wang and Dubois, 2010a).

G. Other Receptors Involved in BLT Receptor Signaling

1. Peroxisome Proliferator-Activated Receptors. Peroxisome proliferator-activated receptors (PPARs) are li-

gand-activated transcription factors that belong to the nuclear hormone receptor superfamily (Michalik et al., 2006). PPARs activate gene transcription associated with metabolism and inflammation, in response to synthetic PPAR ligands developed for the treatment of diabetes and dyslipidemia (Michalik et al., 2006). In addition, LTB₄ has been identified among the endogenous ligands for PPAR α . In transfected HeLa cells, LTB₄ activated PPAR α reporter gene transcription in the micromolar range and bound a fusion protein containing the ligand-binding domain of PPAR α , with a K_d of 90 nM (Devchand et al., 1996). Subsequent studies using different methods have confirmed LTB₄ binding to and activation of PPAR α (Krey et al., 1997; Lin et al., 1999; Narala et al., 2010), although negative results have also been reported (Forman et al., 1997). In addition to results obtained in vitro, a recent study has also demonstrated that mice lacking LTB₄ biosynthesis through 5-LO knockout exhibited reduced PPAR α activation in response to LPS administration in vivo (Narala et al., 2010). The latter results therefore support the observation that endogenous intracellular LTB₄ formation can reach sufficient concentrations for PPAR α activation under inflammatory conditions (Narala et al., 2010).

2. *Vanilloid Transient Receptor Potential V1 Receptor*. The TRPV1 receptor is a ligand-gated, nonselective cation channel, which belongs to a family of TRP channels present exclusively in small sensory neurons and associated with pain. Although capsaicin and other vanilloids are the classic agonists, endogenous ligands derived from lipoxygenase metabolism of arachidonic acid and anandamide have also been reported to activate TRPV1 receptors (Hwang et al., 2000; McHugh et al., 2006). In inside-out patches of cultured dorsal root ganglion, TRPV1 receptors are activated by lipoxygenase products such as 12(S)-HpETE, 15(S)-HpETE, 5(S)-HETE, and LTB₄, whereas LTC₄ is without effect (Hwang et al., 2000). The EC₅₀ for LTB₄-induced TRPV1 activation was 11 μ M, which was 10-fold higher than that obtained for capsaicin in the latter study (Hwang et al., 2000) and substantially lower compared with BLT₁R-mediated LTB₄-induced signaling. In line with these findings, LTB₄ also increased [Ca²⁺]_i in TRPV1-transfected CHO cells, albeit with significantly lower E_{max} and a longer exposure time required to achieve maximum effects compared with capsaicin (McHugh et al., 2006). Indeed, very recently it has also been demonstrated in vivo that both peripheral and spinal administration of RvE1 or RvD1 in mice potently reduces inflammatory pain behaviors, without affecting basal pain perception. These actions are transduced through RvE1-mediated inhibition of TRPV- and TNF- α -induced excitatory postsynaptic current increases in spinal dorsal horn neurons (Xu et al., 2010).

III. CysLT Receptors

A. CysLT Receptor Subtypes

1. *From Cloning CysLT Receptors to Recent Molecular Advances*. The CysLTRs eluded gene cloning with conventional approaches for many years. Eventually, in 1999 two separate groups cloned the first CysLTR (Lynch et al., 1999; Sarau et al., 1999), and in the following year the second receptor subtype was cloned by three different groups (Heise et al., 2000; Nothacker et al., 2000; Takasaki et al., 2000). Hydrophobicity analysis of the deduced primary amino acid sequences demonstrated that both receptors possess seven TM helices organized in a serpentine topology, confirming early studies that provided evidence that cysteinyl LTs were acting through a GPCRs and confirmed pharmacological evidence for CysLTR heterogeneity based on the functional as well as on ligand-binding data (for review of early reports, see Capra, 2004; Capra et al., 2007; Evans, 2003). To date well documented results have been obtained, establishing the existence of two receptor subtypes referred to as CysLT₁ and CysLT₂ (see section III.G). This nomenclature was based on the observations that the CysLT₁ receptor was sensitive to inhibition by classic antagonists, whereas the effects mediated by the CysLT₂ receptor were not inhibited by these antagonists (Labat et al., 1992; Brink et al., 2003). These receptors belong to the rhodopsin family of the GPCR gene superfamily and, in particular, to the purine receptor cluster (within the δ group) of phylogenetically related receptors. In addition to a number of orphan receptors, this group includes receptors that respond to purinergic or pyrimidinergic nucleotides, proteases, and PAF (Fredriksson et al., 2003; Kroeze et al., 2003). Unlike the monoamine or neuropeptide receptors, the receptors belonging to the purine cluster have no clear homologs in invertebrates, suggesting a relatively recent evolutionary origin (Adams et al., 2000). Human CysLT₁ and CysLT₂ receptors share only 38% aa identity, with very low homology in the extreme carboxyl termini. Of interest, human CysLTRs have higher homology with the purinoceptor P2Y_{1/2/6} (32–30% aa identity) or GPR17 (34–32% aa identity) than with the other known LT receptors, the BLT_{1/2} receptors (\leq 27% aa identity).

The human CysLT₁ gene/chromosome location has been mapped on the long arms of chromosome X (Xq13-Xq21), a region lacking asthmatic disease markers (Lynch et al., 1999), whereas CysLT₂ on human chromosome 13 (13q14) (Heise et al., 2000; Takasaki et al., 2000) is near a marker that has been associated with atopic asthma (Cookson, 1999; Kimura et al., 1999).

a. *CysLT₁ Receptor*. The open reading frame of the human CysLT₁ encodes a protein of 337 aa (NCBI Reference Sequence: NP_006630) with a calculated molecular mass of 38 kDa, observed to migrate at a molecular mass of approximately 42 kDa as a monomeric form (Bautz et al., 2001; Figueroa et al., 2001; Ohd et al.,

2003; Hasegawa et al., 2010), although oligomers were often observed (see section III.G). However, other authors observed monomeric migration at different molecular masses, possibly reflecting differences in the cell type, protein/cell maturation, or experimental conditions: 30 to 36 kDa (Sjöström et al., 2001, 2002) and 38 to 40 kDa (Capra et al., 2004). Human CysLT₁R possesses four potential N-glycosylation sites, one in the extracellular N-tail, two in the second extracellular loop, and one in the third extracellular loop, besides many potential protein kinase A and C phosphorylation sites (see section III.D), mostly located in the third intracellular loop and carboxyl terminal (Lynch et al., 1999). The rank order of potency for the cysteinyl LTs is LTD₄ > LTC₄ when tested in different functional assays, such as stimulation of calcium-activated chloride conductance in *Xenopus laevis* oocytes or fluorescence calcium imaging in COS-7, HEK-293, or CHO human CysLT₁-transfected cells. LTE₄ is the less potent agonist acting as a partial agonist. As expected, the LTD₄ functional response is potently inhibited by the selective CysLT₁R antagonists, 3-[[3-[2-(7-chloroquinolin-2-yl)vinyl]phenyl]-(2-dimethylcarbamoyl)ethylsulfanyl] methylsulfanyl] propionic acid (MK-571), zafirlukast, pranlukast, montelukast, and pobelukast (Brink et al., 2003; Evans, 2003; Capra, 2004). Saturation radioligand binding experiments on membranes from COS-7 cells expressing the human CysLT₁R and using [³H]LTD₄ as a labeled ligand demonstrated a single *K_d* of 0.3 nM (Lynch et al., 1999) or high- and low-affinity binding sites with *K_d* values of 0.06 and 6.2 nM (Capra et al., 2005). *B_{max}* has been reported to be approximately 50 fmol/mg membrane protein in both reports.

The genomic organization of the human *CYSLTR1* gene has been obtained by 5'- and 3'-rapid amplification of cDNA ends method, modified to ensure the amplification of only full-length transcripts (Woszczek et al., 2005). The gene consists of five exons that are variably spliced and a single promoter region TATA-less with multiple transcription start sites. Four different CysLT₁R transcripts were identified with a dominant and wide expression of the transcript I, containing exons 1, 4, and 5, with the strongest presence in blood leukocytes, spleen, thymus, lung, and heart (Woszczek et al., 2005). Successive articles reported that *CYSLTR1* contains three exons with the entire open reading frame located in exon 3 and that five splice variants were detected in human leukocytes (Zhang et al., 2006), whereas in human airway SMCs and peripheral blood mononuclear cells (MNCs) three transcripts and, possibly, two putative promoters were found (Duroudier et al., 2007). In summary, multiple splice variants of CysLT₁R exist, and the transcript expression patterns seem to differ from tissues and cell types. At present, the role of alternative splice variants of CysLT₁R is not known. Woszczek et al. (2005) also reported in their study that the promoter region contains several binding sites for transcription factors, such as activator protein-1

(AP-1) and GATA and that CysLT₁R expression is functionally regulated at the transcriptional level by IL-4 through a signal transducer and activator of transcription (STAT)-6 response element localized to the proximal promoter region, confirming former studies by Thivierge et al. (2001) (see section III.B).

b. CysLT₂ Receptor. The open reading frame of human CysLT₂R encodes a protein of 346 aa (NCBI Reference Sequence: NP_065110), which seems to migrate at a molecular mass of 58 kDa in basophil lysates (Gauvreau et al., 2005) and approximately 50 kDa in platelet (Hasegawa et al., 2010) or at approximately 40 to 42 kDa in HUVECs and COS-7 cells transfected with human CysLT₂ cDNA (Carnini et al., 2011). Human CysLT₂R possesses four potential N-glycosylation sites, three of which in the extracellular N-tail, as well as many potential protein kinase A and C phosphorylation sites mostly located in the third intracellular loop and carboxyl terminal (Heise et al., 2000). Ca²⁺ mobilization assay in HUVECs confirmed early observation in recombinant systems that LTD₄ and LTC₄ are equipotent agonists with an identical EC₅₀ of ~35 nM, and lack of sensitivity of the response to the classic CysLT₁R antagonists, montelukast, zafirlukast, and pranlukast, whereas LTE₄ and 6(*R*)-(4-carboxyphenylthio)-5(*S*)-hydroxy-7(*E*),9(*E*),11(*Z*),14(*Z*)-eicosatetraenoic acid (BAY U9773 behave as partial agonists (Lötzer et al., 2003). Equilibrium binding studies in intact HUVECs using [³H]LTC₄ as labeled ligand revealed the presence of a high-affinity binding site with *K_d* of 29 pM and *B_{max}* of 32 fmol/10⁸ cells (Carnini et al., 2011). In CysLT₂-transfected COS-7 cell membranes high- and low-affinity binding sites with *K_d* values of 0.4 and 50 nM or a single site of 4.8 nM were obtained in two independent saturation experiments using [³H]LTD₄ as labeled ligand (Heise et al., 2000).

The genomic organization of the human *CYSLTR2* has also been published recently. Similarly to *CYSLTR1*, the gene has a TATA-less promoter with multiple transcription start sites. Six variably spliced exons have been identified and eight different CysLT₂R transcripts were also identified in endothelial and monocytic cells (Woszczek et al., 2007). It is noteworthy that IFN-γ increased CysLT₂R mRNA expression and calcium signaling in ECs. However, there were no significant changes in gene reporter and mRNA *t*_{1/2} assays in response to this cytokine, suggesting transcriptional control of CysLT₂R mRNA up-regulation by IFN-γ response motifs localized outside of the cloned CysLT₂R promoter region. Stimulation of ECs by cysteinyl LTs induced mRNA and protein expression of early growth response genes 1, 2, and 3 and cyclooxygenase-2 (COX-2) (Woszczek et al., 2007).

2. Receptor Expression Patterns with Functional Significance. The pathophysiological role of cysteinyl LTs in asthma is well documented (Drazen, 2003; Holgate et al., 2003; Sampson et al., 2003; Arm, 2004; Capra et al., 2007; Hallstrand and Henderson, 2010), and results ob-

tained from localization studies are consistent with the antibronchoconstrictive and anti-inflammatory activities of CysLT₁R antagonists (Kemp, 2003; Riccioni et al., 2004; Currie et al., 2005; Capra et al., 2006; Dahlén, 2006; Ducharme et al., 2006; Montuschi et al., 2007; del Giudice et al., 2009). However, the finding of CysLTR expression in other tissues will certainly encourage the discovery of new functions for cysteinyl LTs in other physiological and pathological conditions (Capra et al., 2007).

a. CysLT₁ Receptor. Initial immunohistochemical analysis confirmed the presence of CysLT₁R protein in a series of cells of particular relevance to asthma and atopy such as monocytes and eosinophils but also in pregranulocytic CD34⁺ cells and in subsets of B lymphocytes (Figuroa et al., 2001). Monocytes/macrophages isolated from peripheral blood MNCs express CysLT₁R mRNA either in large excess compared with CysLT₂R transcript levels (Lötzer et al., 2003) or, exclusively, such as in U937 (Capra et al., 2005), a human leukemic monocyte/macrophage cell line. This correlates with the finding that cysteinyl LTs contribute to inflammatory reactions by induction of MCP-1 via the CCR2B receptor in THP-1 cells (Ichihama et al., 2005; Woszczek et al., 2005; Hashimoto et al., 2009). This reported induction by MCP-1 was also observed in another monocytic leukemia cell line and was further supported by the enhanced activation of chemotactic activity observed in human monocytes (Woszczek et al., 2008a). Likewise, in THP-1 cells, montelukast and zafirlukast significantly down-regulated the chemotaxis induced by MCP-1 and p38 MAPK expression (Hung et al., 2006). These data suggest a dominant functional pathway for the interaction between cysteinyl LTs and MCP-1 in a variety of MNCs, including human monocytes. In animal models, inhibition of MCP-1 produces antiatherogenic effects in vivo in a rabbit carotid balloon injury model (Ge et al., 2009).

The expression of CysLTRs in eosinophils was not unexpected (Bandeira-Melo and Weller, 2003), because the contribution of cysteinyl LTs to their accumulation within asthmatic airways has been well documented (Gauvreau et al., 2001; Ohshima et al., 2002; Nagata and Saito, 2003; Saito et al., 2004). In a recent study, the CysLT₁R has been associated with cytokine transduction signals for the up-regulation of eosinophilopoiesis by IL-13 and eotaxin in murine bone marrow (Queto et al., 2010). These data support early reports demonstrating the inhibitory action of CysLT₁R antagonists on eosinophil activation and migration (Virchow et al., 2001; Fregonese et al., 2002; Suzuki et al., 2003; Ueda et al., 2003; Saito et al., 2004; Nagata et al., 2005), as well as on adhesion (Fregonese et al., 2002; Nagata et al., 2002; Kushiya et al., 2006; Meliton et al., 2007; Profita et al., 2008). There is considerable information available to demonstrate the ability of CysLTR antagonists to reduce airway eosinophilia and eosinophil cationic pro-

tein (ECP) in animals (Underwood et al., 1996; Ihaku et al., 1999) and in humans (Pizzichini et al., 1999; Obase et al., 2002; Steinke et al., 2003; Strauch et al., 2003; Laitinen et al., 2005; Kopriva et al., 2006).

CysLT₁Rs are also found to be expressed in B lymphocytes and CD34⁺ hematopoietic progenitor cells (Figuroa et al., 2001). Indeed, early observations demonstrated that LTD₄-stimulate chemotaxis and transendothelial migration of CD34⁺ hematopoietic progenitor cells (Bautz et al., 2001; Mohle et al., 2003) as well as their proliferation (Braccioni et al., 2002; Parameswaran et al., 2004; Boehmle et al., 2009) and that these activities were suppressed by different CysLT₁ receptor antagonists. Altogether these data indicate a physiological role for cysteinyl LTs as autocrine regulators of hematopoiesis corroborated by the expression of LTC₄S in immature myeloid cells (Tornhamre et al., 2003).

Basophils have also been shown to accumulate in the airways of subjects with atopic asthma (Gauvreau et al., 2001), and these authors documented that human basophils express variable levels of functional CysLT₁R. Of interest, they found that prolonged stimulation of cell cultures with LTD₄ reduced the frequency of CD95 Fas receptor expression, an effect that, albeit modest, was reversed by the CysLT₁R antagonist zafirlukast (Gauvreau et al., 2005). These results seem to suggest that the cysteinyl LT/CysLT₁R system might have a direct effect on basophil accumulation in allergic tissues.

MCs are a primary source of cysteinyl LTs (Austen, 2005) after allergic or nonallergic stimulation and, accordingly to their classification as autacoids, CysLTRs are widely expressed in these cells (Mellor et al., 2001; Sjöström et al., 2002) and are responsible for their proliferation and activation (Jiang et al., 2006, 2009; Kaneko et al., 2009). In agreement with this finding, montelukast has been found to significantly reduce the number of MCs in the inflamed paws of mice with collagen-induced arthritis (Shiota et al., 2006).

The expression of both CysLT₁R and CysLT₂R has also been reported in human platelets by RT-PCR, Western blotting, and flow cytometry (Hasegawa et al., 2010). In this report, the authors demonstrate that cysteinyl LTs induced a release of RANTES and that this effect was inhibited by pranlukast, suggesting a novel role for platelets in allergic inflammation (Hasegawa et al., 2010).

In agreement with a role of cysteinyl LTs in asthma, CysLT₁Rs are expressed by a variety of airway mucosal inflammatory cells and the numbers of inflammatory CysLT₁R-expressing cells (eosinophils, neutrophils, MCs, macrophages, and B lymphocytes but not T lymphocytes) significantly increase in subjects with stable asthma and patients hospitalized for asthma exacerbation compared with control subjects (Zhu et al., 2005). Of interest, a strong positive correlation exists between this observation and the augmented numbers of CD45⁺ progenitors (cells expressing the pan-leukocyte marker

CD45 antigen) (Zhu et al., 2005). In addition, human fibroblasts have been shown to express both CysLT₁ (James et al., 2006; Vannella et al., 2007) and CysLT₂ receptors (Vannella et al., 2007). These cells are also known to produce cysteinyl LTs, suggesting a regulation via an autocrine/paracrine secretion of these lipid mediators. Indeed, exogenous administration of LTD₄ but not of LTC₄ was also able to induce proliferation of both murine and human fibrocytes, and CysLT₁R antagonists blocked this mitogenic effect (Vannella et al., 2007). In contrast, there are two reports that evaluated the contribution of cysteinyl LTs to fibroblast-mediated fibrosis and remodeling in chronic hyperplastic eosinophilic sinusitis (Steinke et al., 2004) or in healthy subjects (Yoshisue et al., 2007) and found that fibroblasts did not substantially express CysLT₁R or CysLT₂R, even after priming with IL-4 or IL-13 (Steinke et al., 2004). However, cysteinyl LTs have a broader capability to synergize with epidermal growth factor receptor (EGFR) to increased thymidine incorporation and cell proliferation, effects that, in agreement with the absence of CysLTRs, are not inhibited by specific CysLT₁R antagonists (MK-571 and montelukast) or by the dual antagonist BAY U9773, pointing to a different mechanism/receptor (Yoshisue et al., 2007).

In human nasal mucosa, increased expression of CysLT₁R has been found both at gene and protein levels in blood vessels and in the interstitial vascular ECs, as well as in eosinophils, MCs, macrophages, and neutrophils (Shirasaki et al., 2002, 2006) and in nasal polyps (Chao et al., 2006; Pérez-Novo et al., 2006). Because subjects with aspirin-induced asthma (AIA) have greater airway hyperresponsiveness to the effects of inhaled cysteinyl LTs than those with aspirin-tolerant asthma (ATA) (Arm et al., 1989), Sousa and colleagues (Sousa et al., 2002; Corrigan et al., 2005) hypothesize that this could be due to the elevated expression of CysLT₁R on inflammatory cells. Their study on nasal biopsy specimens from patients with chronic rhinosinusitis and nasal polyps revealed that aspirin-sensitive rhinosinusitis is indeed characterized by increased numbers of nasal inflammatory leukocytes expressing the CysLT₁R. These results have been confirmed (Ozen et al., 2007) and are consistent with two other reports in which the augmented receptor expression was observed for the majority of eosinophils and subsets of MNCs obtained by nasal lavage (Figuroa et al., 2003) or in sputum after allergen challenges in patients with seasonal allergic rhinitis (AR) (Boulay et al., 2010). Finally, CysLT₁ but not CysLT₂ mRNA has been demonstrated in nasal C-fiber neurons, where LTD₄ directly increased the excitability of capsaicin-sensitive guinea pig nasal trigeminal neurons. These observations suggest a novel mechanism for the actions of cysteinyl LTs and offer an explanation for the observed beneficial use of CysLT₁R antagonists in treating nasal allergen-induced neuronal symptoms (Taylor-Clark et al., 2008).

RT-PCR has allowed the demonstration that human saphenous veins express both a functional CysLT₁R, which mediates contractile effects of cysteinyl LTs, but also a CysLT₂R, which, on the contrary, does not seem to be implicated in contraction (Mechiche et al., 2004) and whose functional role remains to be determined (Allen et al., 1992). Human pulmonary veins also express both receptors and although activation of the former induced the release of a contractile factor only partially blocked by CysLT₁R antagonists, the activation of the CysLT₂R released nitric oxide (NO) (Ortiz et al., 1995). In addition, human pulmonary artery vascular SMCs seem to express at least two different receptors, a CysLT₁R and a novel CysLTR subtype, both responsible for vasoconstriction (Walch et al., 2002). Thus, the mechanical effects of LTD₄ on human pulmonary vasculature are complex and involve both direct and indirect mechanisms mediated via at least two, and possibly more, types of cysteinyl LT receptors (Walch et al., 2000).

In the gastrointestinal system, CysLT₁R expression has been documented in the small intestine and colon (Lynch et al., 1999; Sarau et al., 1999). Subsequently, the presence of the CysLT₁R subtype was reported in a nontransformed epithelial intestinal cell line (Ohd et al., 2003), corroborating previous findings for LTD₄-induced signaling in these cells (Grönroos et al., 1995; Thodeti et al., 2000, 2001). In addition, CysLT₁R functions were characterized in colorectal carcinoma cells (Ohd et al., 2003), and low expression of CysLT₁R and high expression of CysLT₂R correlated with high differentiation and good prognosis (Magnusson et al., 2007, 2010). The same results have been also extended to breast cancer cells and patient survival (Magnusson et al., 2011).

b. CysLT₂ Receptor. Localization studies have identified a distinctive expression pattern for human CysLT₂R, despite some overlapping with CysLT₁R. Indeed, expression in heart, particularly in Purkinje fiber cells, myocytes, and fibroblasts derived from atrium and ventricle, brain, and adrenal glands is specific to CysLT₂R (Heise et al., 2000; Nothacker et al., 2000; Takasaki et al., 2000).

Several authors indicated that HUVECs almost exclusively express CysLT₂R (Mita et al., 2001b; Lötzer et al., 2003), which is responsible for the calcium mobilization and contraction evoked in these cells by cysteinyl LTs, as well as by the selective CysLT₂R agonist BAY U9773 (Sjöström et al., 2003; Carnini et al., 2011), for which activation results in a proinflammatory EC phenotype (Uzonyi et al., 2006). ECs are strategically located at the interface with blood circulation where they become exposed to neutrophil- and platelet-derived LTs, a setting that has potential implications for cardiovascular diseases (CVDs). Moreover, previous studies demonstrated that cysteinyl LTs can trigger several functional responses in ECs, such as PAF accumulation and neutrophil adhesion (McIntyre et al., 1986) and secretion of von Willebrand factor and of P-selectin surface expression (Datta et al., 1995). In light of these expression data, the

responses data can be attributed to the CysLT₂R and, accordingly, are not inhibited by selective CysLT₁R antagonists (Pedersen et al., 1997).

Kamohara et al. (2001) were the first to report the presence of a functional CysLT₂R on human coronary artery SMCs. These authors demonstrated that LTC₄ enhanced [Ca²⁺]_i, an effect that was not blocked by CysLT₁R antagonists but blocked by the calcium channel blocker nicardipine. Further significance of cysteinyl LTs involvement in atherosclerosis arises from the observation that cysteinyl LTs induce contractions of human atherosclerotic coronary arteries, whereas nonatherosclerotic arteries are unresponsive (Allen et al., 1998). Taken together, these results suggest that the activation of CysLT₂R can induce profound effects in cardiac as well as in hemodynamic and microcirculatory pathophysiology and that this receptor subtype represents an interesting pharmacological target in the future for CVDs.

Although little expression for CysLT₁R has been reported in brain (Lynch et al., 1999; Sarau et al., 1999), apparent localization has been documented by immunohistochemical analysis in human brains with traumatic injury or tumors (Zhang et al., 2004). In contrast, CysLT₂R mRNA is highly expressed in the central nervous system, with particular concentration in hypothalamus, thalamus, putamen, pituitary, and medulla (Heise et al., 2000) and in small, but not large, vessels in mouse brain (Moos et al., 2008). A number of articles have reported the involvement of either CysLT₁ (Fang et al., 2006) or CysLT₂ (Fang et al., 2007) or both receptors (Sheng et al., 2006; Wang et al., 2006; Huang et al., 2008) in the inflammatory process subsequent to brain vascular insults (vascular ischemia or oxygen deprivation). Spatiotemporal expression of CysLT₂R mRNA in rat brain was observed after focal cerebral ischemia induced by middle cerebral artery occlusion, suggesting that CysLT₂R may be related to the acute neuronal injury and late astrocyte proliferation in the ischemic brain (Fang et al., 2007).

In the immune system, moderate expression of CysLT₂ mRNA was seen in spleen, lymph nodes, and peripheral blood leukocytes (Heise et al., 2000). A comparative study on the levels of CysLTR subtype expression in human peripheral blood leukocytes (eosinophils, neutrophils, monocytes, and T lymphocytes) indicated a significantly high expression for CysLT₂ mRNA in eosinophils (Mita et al., 2001b), suggesting unidentified roles for this receptor in these cells. Mellor et al. (2003) reported that human MCs constitutively express the CysLT₂R, whose proposed function seems to be the production of IL-8. CysLT₂R expression was also reported in basophils (Gauvreau et al., 2005), but a functional role for this protein was not identified, despite flow cytometric analysis, which revealed an expression level equivalent to that of the CysLT₁R. No CysLT₂R expression was found in either undifferentiated

or differentiated promyelocytic HL-60 and U937 cells (Nothacker et al., 2000; Capra et al., 2005).

CysLT₂R was expressed in the majority of eosinophils and in subsets of MCs and MNCs, but not in neutrophils, obtained by nasal lavage of patients with seasonal AR (Figueroa et al., 2003). Sousa et al. (2002) and Corrigan et al. (2005) extended a previous study on CysLT₁R expression in the nasal mucosa of subjects with chronic rhinosinusitis, both AIA and ATA, and found that the distribution of CysLT₂R differs from that of CysLT₁, with a predominance of CysLT₂R on glands and epithelium. They also showed that nasal mucosal inflammatory leukocytes showed no evidence of up-regulation of CysLT₂R in subjects with rhinosinusitis, whether AIA or ATA, compared with control subjects (Corrigan et al., 2005). However, CysLT₂R up-regulation has been demonstrated in nasal polyp tissue and expression was correlated with eosinophilic inflammation (Pérez-Novo et al., 2006). In human lung, the CysLT₂ mRNA signal was high in interstitial macrophages and weak in SMCs (Heise et al., 2000), in which, on the contrary, CysLT₁ mRNA expression was elevated. Of interest, RT-PCR revealed that A549 cells, a human lung adenocarcinoma-derived line with alveolar epithelial cell properties, express mRNA for CysLT₂R but not CysLT₁R (Sloniewsky et al., 2004).

The adrenal gland may represent a novel tissue for future studies on cysteinyl LT functions and CysLT₂R role in modulating the endocrine system because strong expression was detected in medullary pheochromocytes (Lynch et al., 1999; Nothacker et al., 2000).

3. Localization of CysLTRs. The mechanism of action of cysteinyl LTs is thought to be primarily dependent on their specific plasma membrane receptors that, as discussed above, belong to the superfamily of GPCRs. However, a few reports indicate that CysLTR could also be localized to a nuclear compartment, suggesting major unanticipated roles for these receptors in cell signaling and function. Bandeira-Melo et al. (2002b) provided the first evidence for an intracrine CysLTR-induced signaling of eosinophil vesicular transport-mediated IL-4 secretion, which is PTX-sensitive. Furthermore, CysLT₁R was found to be located in the outer nuclear membrane in colon cancer cells and may apparently be translocated into the nucleus after prolonged exposure to the agonist in nontransformed intestinal epithelial cells (Nielsen et al., 2005a). These authors also demonstrated that a nuclear localization sequence (localized in the C tail) is essential for the receptor translocation to the nucleus, as already demonstrated for other GPCRs (Boivin et al., 2008) as well as for other proteins that normally target the nucleus, such as 5-LO (Hanaka et al., 2002). Finally, CysLT₁R expression in myofibroblasts derived from human heart valves exhibits a perinuclear pattern, and LTC₄ increased nuclear [Ca²⁺] in those cells (Nagy et al., 2011).

Because other lipid mediators have been demonstrated to exert biological functions including transcrip-

tional regulation of COX-2 and inducible NO synthase through their nuclear GPCRs (Marrache et al., 2005), one can speculate that the roles for nuclear receptors may be different from those on plasma membrane and that intracellular GPCRs may constitute a distinctive mode of action for gene regulation (Boivin et al., 2008). A recent report has shown that CysLT₁R and CysLT₂R, but also the purinergic P2Y₁₂ receptor, are expressed on eosinophil granule membranes and that cysteinyl LTs stimulated isolated eosinophil granules to secrete ECP. Of interest, although montelukast inhibited ECP release, the P2Y₁₂ receptor antagonist 2,2-dimethyl-propionic acid 3-(2-chloro-6-methylaminopurin-9-yl)-2-(2,2-dimethyl-propionyloxymethyl)-propyl ester (MRS 2395) also inhibited cysteinyl LT-induced ECP release, adding another piece of evidence to the CysLT-P2Y receptor interaction puzzle (Neves et al., 2010) (see sections III.D and III.H).

B. CysLT Receptor Expression and Immunoregulation

Human CysLT₁R expression was up-regulated through augmented transcriptional activity by priming cells with Th2-like cytokines (i.e., IL-5 in eosinophil-differentiated HL-60 cells) (Thivierge et al., 2000) and IL-4 and IL-13 in human monocytes and monocyte-derived macrophages (Thivierge et al., 2001; Shirasaki et al., 2007). The regulation of human CysLT₁R expression by IL-13 has also been reported in the literature for lung fibroblasts (Chibana et al., 2003) and airway SMCs together with TGF- β and IFN- γ , whereas, surprisingly, IL-4 was found to be ineffective (Espinosa et al., 2003). In the latter cells, up-regulation of CysLT₁R by IFN- γ has been demonstrated, and this correlates with increases in LTD₄-induced responses (Amrani et al., 2001). HUVECs express CysLT₁R at a very low level (Sjöström et al., 2001), unless they are subjected to prolonged treatment with IL-1 β (Gronert et al., 2001). The up-regulation by IL-1 β and IFN- γ seems intriguing because these cytokines are generally considered to be counterregulatory, inhibiting both the production and activities of the proallergic Th2-like cytokines. Use of IFN- γ is indeed one of the theoretical approaches to obtain IgE immunomodulation in asthma, albeit adverse effects suggest limited use (Stokes and Casale, 2004). However, there are also investigators who suggest that IFN- γ is likely to be proinflammatory in many aspects of chronic allergic inflammation, evolving our understanding of classic Th2 diseases (Liu, 2000).

Priming human MCs with IL-4 did not result in the up-regulation of CysLT₁R, either at the transcript or the protein level, but rather resulted in the appearance of an apparently new CysLTR also activated by the pyrimidinergic ligand UDP (Mellor et al., 2001). In a subsequent report, the same authors also demonstrated that human MCs primed with IL-4 responded to UDP, LTC₄, and LTD₄ by producing IL-5, TNF- α , and especially large quantities of macrophage inflammatory protein (MIP)-1 β that were inhibited by the CysLT₁R antagonist

MK-571. Nevertheless, human MCs constitutively also express the CysLT₂R, and IL-4 consistently up-regulated surface expression on a fraction of cells (Mellor et al., 2003). Whether IL-4 priming up-regulates a known CysLTR or induces the expression of a new receptor subtype (see section III.G) remains to be established.

A 2- to 3-fold enhancement of CysLT₁R expression was observed in B lymphocytes after exposure to a combination of activating anti-CD40 antibody and IL-4. This enhancement, in turn, induced an increase in responsiveness to LTD₄ in terms of Ca²⁺ flux and up-regulation of IgE and IgG production, which was totally prevented by the selective CysLT₁R antagonist montelukast (Lamoureux et al., 2006). Therefore, Early et al. (2007) showed that IL-4, but not IL-13, was able to significantly induce mRNA and protein concentrations for CysLT₁R from T and B lymphocytes.

CysLTRs can also be immunoregulated by cytokines that play an essential role in down-modulating adaptive and innate immune responses. IL-10, for example, down-regulated mRNA of CysLT₁ and CysLT₂ receptors in a time- and concentration-dependent fashion. In addition, cysteinyl LT-induced activation and chemotaxis of human monocytes and monocyte-derived immature DCs, measured by cytosolic Ca²⁺ flux and immediately early gene expression, was potently decreased by IL-10 and by the CysLT₁ antagonist MK-571 (Woszczek et al., 2008b). Of interest, maturation of DCs with LPS (Thivierge et al., 2006), a classic Toll-like receptor 4 agonist, or zymosan (Thivierge et al., 2009), a Toll-like receptor 2 agonist, down-regulated CysLT₁R mRNA levels and protein expression and reduced functional responsiveness to LTD₄. Indeed, the effect of zymosan was, at least partially, dependent on endogenous production of PGE₂ and IL-10 (Thivierge et al., 2009). Therefore, montelukast prevents the decrease of IL-10 and inhibits NF- κ B activation in inflammatory airway of "asthmatic" guinea pigs (Wu et al., 2006).

Transcript levels of CysLT₂R seem to be up-regulated by the Th2-like cytokine IL-4 in HUVECs (Lötzer et al., 2003) but suppressed by Th1-like (proinflammatory) cytokines, such as TNF- α (Lötzer et al., 2003; Sjöström et al., 2003), LPS, or IL-1 β (Sjöström et al., 2003) in a rapid and partially reversible manner. However, IFN- γ has been found to induce CysLT₂R expression and to enhance the responsiveness to cysteinyl LTs of human ECs (Woszczek et al., 2007), as well as of monocytes, T cells, and B lymphocytes (Early et al., 2007). These data confirm early observations by Fujii et al. (2005), who postulated that CysLT₂R might modulate exacerbations of asthma, as they observed that CysLT₂R expression on eosinophils was up-regulated by IFN- γ and increased during asthma exacerbation, especially in nonatopic subjects. In addition, another proinflammatory cytokine, IL-18, has also been recently postulated to up-regulate CysLT₂R expression in HUVECs at the early

stage of administration, accelerating cell apoptosis (Zhou et al., 2009).

Besides in HUVECs, CysLT₂R expression was also significantly increased in monocytes and eosinophils after IL-4 priming (Early et al., 2007) or IL-13 treatment (Shirasaki et al., 2007). At variance with data reported previously for CysLT₁R, CysLT₂R expression increased after DC maturation induced by LPS, suggesting that these cells may differentially respond to cysteinyl LTs, depending on their maturational stimuli (Thivierge et al., 2006).

These observations suggest that the expression of the CysLTRs may be functionally up-regulated, mainly by Th2-like cytokines (consistent with the classic view of the pathobiological mechanisms of asthma and other allergic diseases), but also by a classic Th1 cytokine (i.e., IFN- γ) at least in some cells (Table 3). This finding raises the possibility that constitutive and inducible receptors may or may not behave in a similar way, prompt-

ing a detailed pharmacological examination of receptors expressed before and after priming.

C. Intracellular Signaling Pathways and Second-Messenger Systems

1. CysLT₁ Receptor. In consideration of the crucial bronchoconstrictor activity of cysteinyl LTs (Hallstrand and Henderson, 2010) and their role in asthma (Capra et al., 2007), intracellular Ca²⁺ mobilization and phosphatidylinositol (PI) metabolism were the obvious signal transduction systems to investigate (for a review of early reports, see Brink et al., 2003; Rovati and Capra, 2007). Upon cloning, LTD₄-induced functional responses in oocytes (Lynch et al., 1999) or HEK-293 cells (Sarau et al., 1999) indicated that, at least in these systems, CysLT₁R is very weakly, if not at all, coupled to a PTX-insensitive G protein (G_{q/11}).

However, an initial study demonstrated in circulating MNCs that cysteinyl LTs modulate Ca²⁺ responses

TABLE 3
Immunoregulation of human CysLTR expression

Receptor	Cytokine	Cell	Effect ^a	Reference
CysLT ₁	IL-4	Monocytes and monocytes-derived macrophages	↑ mRNA; ↑ ; protein; ↑ [Ca ²⁺] _i	Thivierge et al., 2001
			↑ mRNA	Woszczek et al., 2005; Shirasaki et al., 2007
	+ Anti-CD40 antibody	B lymphocytes	↑ mRNA; ↑ protein	Early et al., 2007
		T lymphocytes	↑ [Ca ²⁺] _i ; ↑ IgE/IgG production	Lamoureux et al., 2006
	IL-5	Eosinophil-differentiated HL60	↑ mRNA; ↑ protein	Early et al., 2007
	IL-13	Monocytes and monocyte-derived macrophages	↑ mRNA; ↑ protein; ↑ [Ca ²⁺] _i	Thivierge et al., 2000
			↑ mRNA	Thivierge et al., 2001
	IFN- γ	Lung fibroblasts	↑ mRNA; ↑ , protein; ↑ eotaxin production	Shirasaki et al., 2007
		Airway SMCs	No effect on mRNA; ↑ protein; ↑ cell proliferation	Chibana et al., 2003
		Airway SMCs	↑ mRNA; ↑ protein; ↑ cell stiffness	Espinosa et al., 2003
		Airway SMCs	↑ mRNA; ↑ protein; no effect on cell proliferation	Amrani et al., 2001
	IL-1 β	HUVECs	↑ mRNA	Espinosa et al., 2003
	TGF- β	Airway SMCs	No effect on mRNA; ↓ protein; ↓ cell proliferation	Gronert et al., 2001
	IL-10 (zymosan-induced)	Monocytes and monocyte-derived dendritic cells	↓ mRNA; ↓ [Ca ²⁺] _i and chemotaxis	Espinosa et al., 2003
			↓ mRNA; ↓ [Ca ²⁺] _i and chemotaxis	Woszczek et al., 2008b
CysLT ₂	LPS	Monocyte-derived dendritic cell	↓ mRNA; ↓ protein; ↓ [Ca ²⁺] _i and chemotaxis	Thivierge et al., 2009
			↓ mRNA; ↓ protein; ↓ [Ca ²⁺] _i and chemotaxis	Thivierge et al., 2006
	IL-4	HUVECs	↑ mRNA	Lötzer et al., 2003
		Mast cells	↑ protein	Mellor et al., 2003
	IL-13	B and T lymphocytes, monocytes, eosinophils	↑ mRNA; ↑ protein	Early et al., 2007
		Monocytes	↑ mRNA	Shirasaki et al., 2007
	IFN- γ	Eosinophils (asthmatics)	↑ mRNA; ↑ protein	Fujii et al., 2005
		ECs	↑ mRNA; ↑ [Ca ²⁺] _i	Woszczek et al., 2007
	IL-18	Monocytes, T and B lymphocytes	↑ mRNA; ↑ protein	Early et al., 2007
		HUVECs	↑ mRNA; ↑ protein (first 2 h)	Zhou et al., 2009
	TNF- α	HUVECs	↓ mRNA	Lötzer et al., 2003; Sjöström et al., 2003
				Sjöström et al., 2003
	LPS	HUVECs	↓ mRNA	Sjöström et al., 2003
	IL-1 β	Monocyte-derived dendritic cell	↑ mRNA; ↑ protein	Thivierge et al., 2006
		HUVECs	↓ mRNA	Sjöström et al., 2003
	IL-10	Monocytes and monocyte-derived dendritic cells	↓ mRNA	Woszczek et al., 2008b

^a ↑, up-regulation; ↓, down-regulation; specified are the effects (at mRNA, protein, and functional level).

through a PTX-sensitive G protein ($G_{i/o}$) (Baud et al., 1987). In further reports, investigators have shown that the Ca^{2+} modulation may be through two distinct G proteins, one PTX-sensitive and one insensitive, in monocyte/macrophage U937 cells (Pollock and Creba, 1990; Capra et al., 2003) or in a human epithelial cell line (Sjölander et al., 1990; Adolfsson et al., 1996). Subsequently, CysLT₁R-dependent actin reorganization was shown to be coupled with a PTX-sensitive G protein and to Rho in an intestinal epithelial cell line (Grönroos et al., 1996; Massoumi and Sjölander, 1998; Massoumi et al., 2002) or in bronchial SMCs (Saegusa et al., 2001). Thus, these data confirm CysLT₁R promiscuity in G protein coupling in constitutive systems, in good agreement with the finding that LTD₄ activates distinct signaling pathways differently coupled to G proteins in MNCs (Saussy et al., 1989; Skoglund and Claesson, 1991; Hoshino et al., 1998; Capra et al., 2003) or intestinal epithelial cells (Grönroos et al., 1998; Paruchuri and Sjölander, 2003; Nielsen et al., 2005b). Among these pathways several groups have demonstrated the activation of MAPK by CysLT₁R in THP-1 cells (Hoshino et al., 1998), renal mesangial cells (McMahon et al., 2000), intestinal epithelial cells (Paruchuri et al., 2002), monocyte/macrophage U937 cells (Capra et al., 2004), astrocytes (Ciccarelli et al., 2004), colon cancer cells (Parhamifar et al., 2005), MCs (Jiang et al., 2006), and airway SMCs (Ravasi et al., 2006). Cysteinyl LTs have been shown to induce proliferation in a variety of cells, such as human hematopoietic cell lines (Snyder et al., 1989; Braccioni et al., 2002; Parameswaran et al., 2004), airway epithelial cells (Leikauf et al., 1990), vascular (Porreca et al., 1995, 1996; Kaetsu et al., 2007) and airway SMCs (Cohen et al., 1995; Panettieri et al., 1998; Espinosa et al., 2003; Bossé et al., 2008), glomerular mesangial cells (Kelefiotis et al., 1995), intestinal epithelial cells (Paruchuri and Sjölander, 2003), astrocytes (Fang et al., 2006; Huang et al., 2008) and fibrocytes (Vannella et al., 2007).

There are many possible pathways through which GPCRs may induce ERK1/2 activation, one of which requires the transactivation of a growth factor receptor. Indeed, a first report suggested that LTD₄ synergizes with the insulin growth factor axis to induce airway SMC proliferation (Cohen et al., 1995), involving proteolysis of airway SMC-produced inhibitory insulin growth factor-binding proteins by LTD₄-induced MMP-1 (Rajah et al., 1996). In the same cellular system, LTD₄ has been demonstrated to induce phosphorylation of apoptosis signal-regulating kinase 1 (Kumasawa et al., 2005), a kinase upstream of c-Jun NH₂-terminal kinase (JNK) and p38 MAPK, which in turn regulates transcription factor AP-1, an essential step for regulation of cell proliferation and differentiation. In renal mesangial cells, LTD₄-induced proliferation requires ERK1/2 and p38 activation and is dependent on PI3K and PKC (McMahon et al., 2000). LTD₄ also transactivates the plate-

let-derived growth factor receptor β , which is a process associated with c-Src recruitment and Ras activation, an effect insensitive to PTX and apparently related to CysLT₁R activation (McMahon et al., 2002). LTD₄-induced airway SMC proliferation was also demonstrated to require transactivation of the EGFR through generation of reactive oxygen species (Ravasi et al., 2006). It is noteworthy that very recently LTD₄ has been demonstrated to transcriptionally activate VEGF production via CysLT₁R, with the involvement of JNK, ERK, the AP-1 complex, and Sp1 (Poulin et al., 2011). Taken together, these findings suggest that cysteinyl LTs may be important in the process of airway remodeling and potentially provide a previously unknown benefit of using LTRAs in the prevention or treatment of chronic asthma, albeit long-term studies aimed to determine its effects on airway remodeling are still lacking. Finally, in human MCs, LTD₄ enhanced proliferation in a CysLT₁- and ERK-dependent manner, which in turn required transactivation of c-kit (Jiang et al., 2006).

However, in THP-1 cells LTD₄ has been postulated to activate MAPK through a PKC-Raf-1-dependent pathway (Hoshino et al., 1998), whereas in differentiated U937 cells ERK1/2 activation involves a Ras-GTP-dependent pathway, phospholipase C, and Ca^{2+} -dependent tyrosine kinase(s) (Capra et al., 2004). In addition, LTD₄ has been shown to induce proliferation and migration of mouse embryonic stem cells via a mechanism involving STAT-3, PI3K, glycogen synthase kinase-3 β / β -catenin phosphorylation and calcineurin expression (Kim et al., 2010).

In intestinal epithelial cells, LTD₄ has been shown to increase cell survival and proliferation (Ohd et al., 2000; Paruchuri and Sjölander, 2003), activating MAPK through a Ras-independent but PKC ϵ -dependent pathway (Paruchuri et al., 2002), and to increase cell mobility via a PI3K/Rac signaling pathway (Paruchuri et al., 2005). Furthermore, the antiapoptotic effect involves the prevention of caspase 8 activation and Bid cleavage (Wikström et al., 2003a), as well as COX-2 transcription and Bcl-2 up-regulation mediated through a PTX-sensitive G protein and the ERK-1/2 pathway (Wikström et al., 2003b). Indeed, LTD₄ exposure, through PI3K-dependent phosphorylation of glycogen synthase kinase-3 β induced a β -catenin translocation to the nucleus, where there is an elevation of the promoter activity of the TCF/LEF family of transcription factors, and to the mitochondria, where the action is associated with the cell survival protein Bcl-2 (Mezhybovska et al., 2006). CysLT₁R involvement in colon cancer cell proliferation was also shown via endogenous production of cysteinyl LTs that, through cytosolic phospholipase A₂ activation (Parhamifar et al., 2005), mediates an autocrine survival and proliferation signal in nontumor- and tumor-derived epithelial cells (Paruchuri et al., 2006). To the best of our knowledge, there is only one report suggesting that cysteinyl LTs may, on the contrary, inhibit the

growth of a human cell line (i.e., the mammary cancer MCF-7 cells) (Przylipiak et al., 1998).

Proliferation is not the only effect induced by MAPK activation. For example, in monocytes, LTD₄ induced p38 phosphorylation (Woszczek et al., 2008a), a pathway involved in the regulation of immediate-early gene expression. In a human epithelial cell line, CysLT₁R activation has been shown to lead to either STAT-1 phosphorylation through PKC and ERK1/2 activation, causing enhanced intercellular cell adhesion molecule-1 expression and eosinophil adhesion (Profita et al., 2008), or to up-regulate mucin gene *MUC2* transcription via a signaling pathway involving PKC and NF- κ B (Suzuki et al., 2008). In this respect, NF- κ B, a transcription factor largely involved in inflammation and in regulating the immune response, has been demonstrated to be involved in the CysLT₁R transduction pathway by different groups. In isolated lung MNCs, for example, LTD₄ activated NF- κ B and induced production of RANTES (Kawano et al., 2003), whereas in THP-1 and in human DCs CysLT₁R engagement induced AP-1- and NF- κ B-dependent IL-8 expression (Thompson et al., 2006), as well as increased MCP-1 (Hashimoto et al., 2009). In partial agreement with these data LTD₄ has been demonstrated to induce AP-1, but not NF- κ B signaling in intestinal epithelial cells (Bengtsson et al., 2008). Therefore, montelukast inhibited NF- κ B activation in THP-1 cells in a dose-related manner (Maeba et al., 2005), and TNF- α -stimulated IL-8 expression through changes in NF- κ B p65-associated histone acetyltransferase activity in differentiated U937 cells (Tahan et al., 2008).

However, three distinct studies have reported that LTD₄ did not induce NF- κ B nuclear translocation. In contrast, pranlukast inhibited NF- κ B activation (Ichiyama et al., 2003), TNF- α production (Tomari et al., 2003), or *MUC2* gene transcription (Ishinaga et al., 2005), effects that were suggested to be independent from CysLT₁R antagonism. A different study also reported that pranlukast inhibited IL-5 production in various cells irrespective of their CysLT₁R mRNA expression (Fukushima et al., 2005), again suggesting that the compound may have other activities beyond CysLT₁R antagonism. Furthermore, montelukast and zafirlukast have been demonstrated to inhibit the effects of nucleotides acting at different P2Y receptors (P2Y_{1,2,4,6}) (Mamedova et al., 2005), although in a noncompetitive manner. These observations have recently been confirmed by another report demonstrating that montelukast and zafirlukast, acting in a concentration-dependent manner, can inhibit non-CysLT₁R-mediated proinflammatory reactions in human monocytes while inhibiting UDP-induced Ca²⁺ mobilization (Woszczek et al., 2010). Taken together, these data demonstrate non-CysLTR-related activities for these classic LTRAs. Thus, the therapeutic effects of these compounds must be considered with some reserve.

Another interesting cellular function that emerged to be modulated by CysLT₁R is the up-regulation of β integrins. Massoumi and Sjölander (2001) first demonstrated that in intestinal epithelial cells LTD₄ induced a Src-dependent rapid tyrosine phosphorylation of vinculin, as well as PKC-dependent up-regulation of active β 1 integrins on the cell surface and a consequent enhanced adhesion of cells to collagen IV. Furthermore, in Caco-2 cells, LTD₄ controlled adhesive properties and migration by up-regulating COX-2 and stimulating PGE₂-induced expression of α 2 β 1 integrins (Massoumi et al., 2003). In another study, LTD₄ was demonstrated to rapidly induce focal adhesion kinase-related tyrosine kinase phosphorylation and significantly up-regulated α 4 β 1 and α 5 β 1 integrin-dependent adhesion of both primitive and committed hematopoietic stem and progenitor cell (Boehmle et al., 2009).

In some systems, CysLT₁R activation can contribute to the propagation of the inflammatory reaction by the release of various inflammatory mediators and cytokines. Thus, although cytokines may regulate CysLTR expression, cysteinyl LTs may, in turn, induce their release in an amplifying circuit of inflammation. For example, in U937 cells, LTD₄ triggered a rapid release of arachidonic acid metabolites into the culture medium, an effect that was suppressed by the CysLTR antagonist 2(*S*)-hydroxyl-3(*R*)-carboxyethylthio)-3-[2-(8-phenyloctyl) phenyl] propanoic acid (SKF 104353), by the topoisomerase I inhibitor camptothecin, and by staurosporine (Mattern et al., 1990). Several different groups have reported CysLT₁R-induced release of Th2 cytokines, such as IL-4 from cord blood-derived eosinophils (Bandeira-Melo et al., 2002a,b), IL-5 from MNCs (Nabe et al., 2002; Frieri et al., 2003; Faith et al., 2008), chemokines, such as RANTES, from MNCs (Kawano et al., 2003) or platelets (Hasegawa et al., 2010), IL-8 from THP-1 cells (Thompson et al., 2006), and MIP-1 α and MIP-1 β (Ichiyama et al., 2009) or IL-11 (Lee et al., 2007a) from epithelial cells. Of interest, LTC₄ and LTD₄, but not LTE₄, enhanced TNF- α -induced MMP-9 production in human MNCs (Ichiyama et al., 2007), an effect that, although inhibited by montelukast, does not seem to be CysLT₁R-dependent in eosinophils (Langlois et al., 2006). Finally, a combination of LTD₄ and IL-5 or granulocyte macrophage-colony-stimulating factor synergistically induced TGF- β 1 expression in eosinophils (Kato et al., 2005), whereas LTC₄ induced TGF- β 1 production in airway epithelial cells (Perng et al., 2006) or in a time- and concentration-dependent manner in CysLT₁R-transfected HEK-293 cells (Bossé et al., 2008).

Thus, montelukast and/or pranlukast significantly reduced in OVA-treated mice the increased IL-4 and IL-13 (Henderson et al., 2002; Lee et al., 2007a) in BAL fluid, IL-11 and TGF- β 1 in BAL and lung tissues (Lee et al., 2007a), IL-4, IL-5, IL-13, and eotaxin in BAL, and TGF- β gene expression in GATA-3-overexpressing mice (Kiwamoto et al., 2011), thereby preventing airway in-

flammation, bronchial hyperresponsiveness, and airway fibrosis. Of interest, LTD₄ in HEK-293 cells stably transfected with the CysLT₁R can transcriptionally activate furin production with consequent maturation of furin, a proprotein convertase involved in the maturation/activation of several substrates implicated in the remodeling processes (Thompson et al., 2008b).

Treatment with montelukast decreased the amount of IL-4 but increased the amount of INF- γ mRNA expression in the lungs of IL-2-treated OVA-sensitized rats (Nag et al., 2002), decreased tissue inflammation, decreased total cell count and number of eosinophils and lymphocytes in BAL and inhibited the increase in endothelin-1 and INF- γ after intratracheal Sephadex provocation in rats (Finsnes et al., 2002). Furthermore, montelukast significantly inhibited LPS-induced IL-6, TNF- α , and MCP-1 production in the peripheral blood MNCs of control subjects and patients with asthma (Maeba et al., 2005), whereas pranlukast decreased the levels of many cytokines and chemokines (IL-4, IL-5, IL-1 β , TNF- α , RANTES, and IL-8) in nasal mucosa, leading to improvement in patients with nasal symptoms (Ueda et al., 2003).

2. CysLT₂ Receptor. Obtaining detailed information about signal transduction systems involved in CysLT₂R activation was hampered by the absence of selective antagonists, at least until a short time ago (Huang et al., 2008; Wunder et al., 2010). Thus, most of the data still rely on either recombinant systems or have been obtained in ECs that predominantly express CysLT₂R. As in the case of the CysLT₁R, the CysLT₂R also seems to be mainly coupled to PI hydrolysis and intracellular Ca²⁺ mobilization through a PTX-insensitive G protein (G_{q/11}) in recombinant systems (Heise et al., 2000). CysLT₂R activation in HUVECs causes an increase in [Ca²⁺]_i (Lötzer et al., 2003), confirming early reports in which LTC₄ and LTD₄ were demonstrated to induce a rapid [Ca²⁺]_i transient that was inhibited by the receptor antagonist pobilukast (Heimbürger and Palmblad, 1996), which, despite being considered a CysLT₁R antagonist, is apparently a dual CysLT₁/CysLT₂R antagonist (G. E. Rovati, unpublished observations). Furthermore, in the same cells cysteinyl LTs induce myosin light-chain kinase activation, stress fiber formation, and EC contraction that are totally PTX-insensitive (Carnini et al., 2011). In contrast, in human MCs under conditions in which CysLT₁R is blocked by MK-571 pretreatment, CysLT₂R stimulation elicited secretion of IL-8 through p38 activation, an effect completely inhibited by PTX (Mellor et al., 2003).

As mentioned previously, in ECs of human vasculature CysLT₂R induced relaxation (Allen et al., 1992), an effect that was successively linked to the formation of NO, at least in human pulmonary arteries and veins (Ortiz et al., 1995). In addition to direct action on the vascular tone, cysteinyl LT-induced activation of ECs may also lead to changes in the transcriptional activity.

In HUVECs, LTD₄ induces endothelial P-selectin expression (Pedersen et al., 1997), strongly stimulates expression of MIP-2 (Zhao et al., 2004), and together with thrombin up-regulates 37 early inducible genes, among which the most strongly induced are early growth response 1 (*EGR1*), nuclear receptor subfamily 4 group A transcription factors, E-selectin, CXC ligand 2, IL-8, a disintegrin-like and metalloprotease (repolysin type) with thrombospondin type 1 motif 1 (*ADAMTS1*), Down syndrome critical region gene 1 (*DSCR1*), tissue factor, and COX-2 (Uzonyi et al., 2006). IL-8 induction has been studied in more detail, demonstrating that in HEK-293 cells stably transfected with CysLT₂R LTC₄ transcriptionally activates its production through induction of NF- κ B and AP-1 transcription factors (Thompson et al., 2008a). However, at variance with the results in HUVECs, a recent article suggested that in EA.hy926 cells, a human EC line, LTD₄ induced the phosphorylation of ERK1/2, but not that of p38 or JNK and that these effects were blocked by the CysLT₁R antagonist montelukast or by the dual antagonist BAY U9773, but not by a novel CysLT₂R antagonist referred to as Bay cysLT₂ (Yuan et al., 2009).

D. Desensitization and Cross-Talk of CysLT Receptors

Early reports showed that in rat basophilic leukemia cells (Vegesna et al., 1988) and in differentiated U937 cells (Winkler et al., 1988; Pollock and Creba, 1990) treatment with phorbol 12-myristate 13-acetate reduced LTD₄-induced PI metabolism and [Ca²⁺]_i mobilization, whereas inhibitors of PKC selectively enhanced LTD₄-induced [Ca²⁺]_i transients (Winkler et al., 1990). These observations suggested for the first time that PKC might play a role in determining the responsiveness of CysLT₁R. Indeed, native human CysLT₁R has been demonstrated to be the target for unidirectional extracellular nucleotide-mediated heterologous desensitization (Capra et al., 2005). In fact, ATP/UDP-induced CysLT₁R desensitization, which was sensitive to PKC inhibition, did not cause receptor internalization and induced a faster recovery of CysLT₁R functionality with respect to LTD₄-induced homologous desensitization. The latter, which was not sensitive to PKC activation by phorbol 12-myristate 13-acetate, induced a fast receptor trafficking and down-regulation, and has been shown to most likely depend on GRK2 activation. Of interest, activation of the CysLT₁R by LTD₄ had no effect on P2Y receptor responses (Capra et al., 2005).

In addition, heterologous desensitization of CysLT₁R is mediated not only by G_{q/11}-coupled receptors but also by G_s-coupled receptors [i.e., β_2 -adrenoreceptors (β_2 AR), histamine H_{1/2} and prostaglandin EP_{2/4} receptors] in differentiated U937 cells and human monocytes, this time through activation of PKA (Capra et al., 2010). Of interest, heterologous desensitization seems to affect mostly the G_i-mediated signaling of the CysLT₁R (Capra et al., 2005, 2010).

However, Naik et al. (2005) reported that agonist-induced internalization of recombinant human CysLT₁R expressed in HEK-293 cells is GRK/arrestin-independent and significantly PKC-dependent. They also demonstrated that mutation of putative PKC phosphorylation sites in the C-tail of the receptor reduced internalization and increased the signaling, significantly attenuating the effects of PKC inhibition. These findings may reflect the use of recombinant systems that produce varying results, depending on cell type and G protein availability, especially when dealing with GPCRs (Kenakin, 1997). In addition, both PKC α and PKC ϵ have been shown to be activated and involved in the regulation of the LTD₄-induced Ca²⁺ signal in human SMCs (Accomazzo et al., 2001) and intestinal epithelial cells (Thodeti et al., 2001). Therefore, in human airway SMCs, PKC inhibition augmented LTD₄-stimulated contraction and increased PI hydrolysis and Ca²⁺ flux, confirming that PKC can regulate CysLT₁R responses (Deshpande et al., 2007). Such an integrated network presumably tunes the strength and duration of the inflammatory signals, thereby leading to fine regulation of the physiological responses.

Although a phylogenetic relationship exists between P2YR and CysLTR on the basis of sequence alignment followed by evolutionary analyses (Fredriksson et al., 2003; Kroeze et al., 2003), functional relationships between cysteinyl LT/CysLTR and purine/P2YR systems are still a matter of debate. Mellor et al. (2001, 2002) first suggested that UDP is also able to activate CysLTRs and that UDP and LTD₄ mediated ERK activation and cytoprotection, implying a cysteinyl LT-mediated autocrine loop (Jiang et al., 2009). However, UDP was not able to compete for binding sites labeled by [³H]LTD₄ in COS-7 cells transiently expressing hCysLT₁R. These data, together with the lack of cross-desensitization between CysLT₁R and P2Y receptors, seem to exclude the involvement of a CysLTR/P2YR heterodimer (Capra et al., 2005). These observations have been recently confirmed by another group using receptor desensitization and small interfering RNA experiments in monocytes and CysLT₁R-transfected HEK-293 cells. These investigators reported that LTD₄ and UDP were acting on separate receptors (Woszczek et al., 2010). On the other hand, Nonaka et al. (2005) first reported that LTE₄ acts as an agonist at the P2Y₁₂ receptor, data recently confirmed by a different laboratory (Fredman et al., 2010), which seemed to corroborate the demonstration of LTE₄-induced pulmonary inflammation mediated through the P2Y₁₂ receptor (Paruchuri et al., 2009). In conclusion, a number of investigations demonstrated a close interplay between these two receptor systems, a topic that may have an impact on the development of therapeutic drugs (see section III.H).

The purinergic receptor, however, is not the only receptor system shown to interact with the CysLTRs. A number of studies have reported that LTRAs used as add-on therapy decrease the need for β_2 -agonists (Na-

than et al., 1998; Noonan et al., 1998; Jarvis and Markham, 2000; Virchow et al., 2000; Keam et al., 2003; Vaquerizo et al., 2003; Deykin et al., 2007; Borderias et al., 2007) and that a positive association exists between a CysLTR antagonist and a β_2 -agonist in controlling asthma symptoms, particularly in patients homozygous for the glycine-16 β_2 AR polymorphism, which predisposes them to agonist-induced down-regulation and desensitization of the β_2 AR (Lipworth et al., 2000). The response to β_2 -agonists is reduced in asthmatic airways, and this desensitization has been postulated to be due in part to inflammatory mediators such as cysteinyl LTs (Song et al., 1998; Milanese et al., 2005). Indeed, LTD₄, through CysLT₁R activation, induced β_2 AR desensitization in human airway SMCs in vitro, an effect again mediated by the PKC pathway (Rovati et al., 2006). Another interesting aspect of CysLTR cross-talk is the growth factor receptor transactivation, an aspect already discussed in section III.C.

E. CysLT Receptor Functional Analysis through Altered Gene Expression

1. Gene Disruption. In 2001, a short isoform and a long isoform of mCysLT₁R were identified in the mouse (Maekawa et al., 2001; Martin et al., 2001). Comparison of the human and the mouse CysLT₁R cDNAs demonstrated that human transcript II contains sequences equivalent to the mouse short isoform (Woszczek et al., 2005). Both cDNAs, the human transcript II and the mouse short isoform, are less preferentially expressed (Woszczek et al., 2005). At the same time, the mCysLT₂R was cloned and two 5'-untranslated region splice variants were identified, with the short form lacking exon 3 as the predominant transcript (Hui et al., 2001). A pharmacological difference was also noted between mouse and human CysLT₂R. Pranlukast, a specific inhibitor for hCysLT₁R, antagonized mCysLT₂R responses at concentrations of 10 μ M, as determined by [Ca²⁺]_i elevation and receptor-induced promoter activation (Ogasawara et al., 2002).

Soon thereafter, Maekawa et al. (2002) generated CysLT₁R-deficient mice by targeted gene disruption; this resulted in loss of both isoforms of the receptor. Peritoneal macrophages from wild-type mice, which expressed both CysLT₁R and CysLT₂R, responded strongly to LTD₄ and slightly to LTC₄ in a Ca²⁺ mobilization assay, whereas those from mutant mice responded to neither ligand. Furthermore, the same authors observed that plasma protein extravasation, but not neutrophil infiltration, was significantly suppressed in CysLT₁R-null mice after zymosan-induced peritonitis or IgE-mediated passive cutaneous anaphylaxis, demonstrating that in acute inflammation the microvasculature responds through the CysLT₁R to cysteinyl LTs generated in vivo by either monocytes/macrophages or MCs. The finding that CysLT₁R-null mice were not protected against chronic injury induced by bleomycin suggested a proinflammatory role for the CysLT₂R in the

chronic response. This finding was corroborated by the observation that bleomycin-induced pulmonary inflammation with fibrosis is significantly attenuated in LTC₄S-null mice but markedly aggravated in CysLT₁R-null mice (Beller et al., 2004a). The same group of researchers examined this issue by generating CysLT₂R-deficient mice (Beller et al., 2004b) and found that CysLT₂R is responsible for mediating the contribution of the cysteinyl LTs to bleomycin-induced chronic pulmonary inflammation and fibrosis. In conclusion, these authors unexpectedly found that CysLT₁R does not mediate the signal for chronic inflammation and fibrosis. They propose that CysLT₁R is responsible for bronchoconstriction, for microvasculature leakage in acute inflammation, and for a counteracting role in chronic inflammation, whereas the CysLT₂R is the receptor providing the signal for chronic inflammation. Furthermore, CysLT₂R-targeted gene disruption revealed a significant reduction in vascular permeability (Beller et al., 2004b). These data have been further confirmed in transgenic mouse models (see below).

GPR17-deficient mice sensitized and challenged with dust mite exhibited markedly increased pulmonary inflammatory and serum IgE responses compared with those of wild-type mice. In contrast, a reduced response to this intervention was observed in mice lacking CysLT₁R. These findings reveal a constitutive negative regulation of CysLT₁R functions by GPR17 in both the antigen presentation and downstream phases of allergic pulmonary inflammation (Maekawa et al., 2010), confirming the *in vitro* observation of an interplay between GPR17 and CysLT₁R (Maekawa et al., 2009) (see section III.H).

2. CysLT Receptor Transgenic Models. A transgenic mouse specifically overexpressing the human CysLT₁R in SMCs via the α -actin promoter was generated to explore the importance of increased cysteinyl LT signaling in airway function. This transgenic model overcame the problem of mice and isolated murine tracheal rings having a minimal bronchoconstrictor response to direct LT challenge compared with that of guinea pigs or humans (Dahlén et al., 1980; Ashida et al., 1987; Martin et al., 1988). Mice were sensitized by intraperitoneal injections with *Aspergillus fumigatus* to obtain a model of allergic airway inflammation. The authors observed that in transgenic mice allergen-induced airway hyperresponsiveness was significantly enhanced after LTD₄ challenge, thus indicating that overexpression of human CysLT₁R on SMCs leads to smooth muscle hyperresponsiveness (Yang et al., 2004).

Hui et al. (2004) have generated mice in which the human CysLT₂R is overexpressed in ECs and reported the effects on endothelial integrity and blood pressure regulation mediated by this receptor subtype *in vivo*. These researchers observed that, in CysLT₂R transgenic mice, the permeability response to exogenous LTC₄ and to endogenous cysteinyl LTs evoked by passive cutane-

ous anaphylaxis was augmented and that this enhanced vascular permeability is controlled via Ca²⁺ signaling and takes place via a transendothelial vesicle transport mechanism as opposed to a paracellular route (Moos et al., 2008). Furthermore, the rapid, systemic pressor response to intravenous LTC₄ was diminished coincidentally with augmented production of NO (Hui et al., 2004). The same group also observed that overexpression of the hCysLT₂R in mice aggravates myocardial ischemia-reperfusion injury by increasing endothelial permeability and exacerbating inflammatory gene expression, leading to accelerated left ventricular remodeling, induction of peri-infarct zone cellular apoptosis, and impaired cardiac performance (Jiang et al., 2008).

F. Pharmacogenetics of CysLT System

The characterization of the genes encoding the cysteinyl LT system, including the *CysLTR1* and *CysLTR2* genes, has advanced the study of CysLTR pharmacology and the GPCR pharmacogenomics of inflammatory disease (Thompson et al., 2005). Furthermore, many of the genes encoding proteins involved in the synthesis and signaling pathways of the cysteinyl LTs are polymorphic and are of interest in genetic studies of asthma (Silverman et al., 2001; Palmer et al., 2002; Israel, 2005).

1. CysLT₁ Receptor Pharmacogenetics. The CysLT₁R is a candidate gene in atopic asthma because drugs that act as high-affinity antagonist ligands of the CysLT₁R, such as montelukast, zafirlukast, and pranlukast, have been shown to have a beneficial therapeutic effect in some cases of atopy that result in asthma (for reviews on LTRAs in therapy, see Bousquet et al., 2009; Diamant et al., 2009; Dunn and Goa, 2001; Keam et al., 2003; Wahn and Dass, 2008), allergic rhinitis (AR), or rhinosinusitis (Grayson and Korenblat, 2007) (see section III.I.1). Moreover, approximately 20% of patients report no change in symptoms during treatment with these agents (Drazen et al., 1999, 2000; Israel, 2005). This finding suggests that in some patients with asthma, the pathway regulating airway cysteinyl LT activity may not be activated with the clinical symptoms of asthma resulting from the actions of other mediators, which would lead to the clinical phenotype of resistance to LTs modifiers (Asano et al., 2002; Lima et al., 2006; Telleria et al., 2008; Tantisira et al., 2009; Langmack and Martin, 2010).

Although the CysLT₁R gene may harbor inactivating mutations in some populations, there are many more variants of the CysLT₂R (Thompson et al., 2003). For example, in studies of the people living on the isolated south Atlantic island of Tristan da Cunha, two variants of the CysLT₁R have been identified, an I206S variant and an activating G300S variant (Thompson et al., 2007). Although the G300S variant was found to be a mildly activating in response to LTD₄ *in vitro*, it was nonetheless associated with atopy in the Tristan da Cunha population.

Furthermore, a number of SNPs in the promoter region of the *CYSLTR1* gene have been found by different groups. Some SNPs were not associated with either the development of asthma/rhinitis (Choi et al., 2004; Zhang et al., 2006) or the response to treatment (Lee et al., 2007b), whereas others, in particular the $-927T > C$ polymorphism (Arriba-Mendez et al., 2006; Hao et al., 2006; Sanz et al., 2006; Al-Shemari et al., 2008; Bizzantino et al., 2009), have been postulated to cause differences in transcriptional activity that may be predictors of disease risk (Duroudier et al., 2007; Hong et al., 2009), or treatment response (Kim et al., 2007b) or be associated with AIA (Kim et al., 2006b, 2007a).

As mentioned before, Lynch et al. (1999) mapped the CysLT₁ gene to the long arm of the human X chromosome. Therefore, Ohd et al. (2003) found a significantly higher frequency of CysLT₁R staining in tissues from male patients affected by colorectal adenocarcinoma, suggesting the presence of allele-dependent dysregulation or sex-specific transcriptional subordination. Although there are four SNP variants in the promoter region of the *CYSLTR1* gene, two of the haplotypes, termed CAAC and TGGC, constitute more than 95% of the alleles noted in small population samples. There was no predisposition in patients with asthma or rhinitis to have one haplotype or the other. However, among women with asthma who were homozygous for the CAAC haplotype, there was a significantly higher expression of the CysLT₁R transcript I than in women who had the CAAC/TCGC complex genotype; transcript II levels were also significantly lower than those in healthy women homozygous for the CAAC haplotype. These data are concordant with previous findings that TCG and CAA haplotypes in the promoter region are associated with different transcriptional activity (Zhang et al., 2006). Of interest, in a recent report of the British 1958 birth cohort, data suggested that the *CYSLTR1* gene promoter polymorphisms might influence the risk of atopy in the female white population with suggestive evidence of heterozygote vigor (Duroudier et al., 2009).

2. CysLT₂ Receptor Pharmacogenetics. The CysLT₂R is also a candidate gene for asthma and atopy because it maps to a region of chromosome 13q14 that has been linked to asthma (Kimura et al., 1999) and atopy (Daniels et al., 1996). Specific CysLT₂R antagonists have only recently been reported (Huang et al., 2008; Wunder et al., 2010), and thus the pharmacological importance of CysLT₂R antagonism in asthma or atopy is yet to be established. However, the development of drugs that target the CysLT₂R may be useful not only for asthma, given that approximately 20% of patients fail to respond to CysLT₁R agents, particularly when the CysLT₂R is also polymorphic, but also for cardiovascular diseases (Funk, 2005; Moos and Funk, 2008; Riccioni et al., 2008).

The Tristan da Cunha study has identified an atopy associated with the M201V variant, which, unlike the G300S CysLT₁ variant, is partially inactivating in terms

of $[Ca^{2+}]_i$ signaling (Thompson et al., 2003) and has been demonstrated to have a reduced affinity for LTC₄ and particularly for LTD₄, an impairment of IL-8 trans-activation as well as NF- κ B and JNK phosphorylation (Brochu-Bourque et al., 2011). This association of the CysLT₂R M201V variant with airway disease has been independently replicated in a large outbred population (Pillai et al., 2004). Transmission disequilibrium testing in 137 Japanese asthmatic families revealed that the $-1220A > C$ polymorphism of the *CYSLTR2* gene is associated with the development of asthma (Fukai et al., 2004), whereas four other sequence variants (either in the 5'- or 3'-flanking region or downstream of the gene) are associated with AIA (Park et al., 2005) and have been linked to altered CysLT₂R expression (Shin et al., 2009). It is noteworthy that two other *CYSLTR2* gene variants, in association with an *ALOX5* polymorphism, have been shown to increase the response to montelukast (Klotsman et al., 2007).

The fact that CysLT₁R and CysLT₂R are both polymorphic in some individuals suggests that if they are coexpressed on inflammatory cells, they may functionally alter cysteinyl LT signaling. If, like many GPCRs, the CysLT₁R and CysLT₂R form functional dimers with unique pharmacological properties (Jiang et al., 2007), the CysLT₂R may also play a role in the CysLT₁R pharmacology (see section III.G). Paradoxically, in the inbred Tristan da Cunha population the activating CysLT₁R G300S variant and the inactivating CysLT₂R M201V variant seem to interact to confer risk for atopy. In this sample, all double heterozygotes were atopic. General linear modeling indicated that the CysLT₁R and CysLT₂R genotypes were independently associated with atopy and asthma phenotypes. The gene-gene interaction, therefore, presents as being consistent with an additive effect that is highly associated with atopy (Thompson et al., 2007).

G. Homodimers or Heterodimers?

Some experimental evidence indicates the possibility that CysLTR might exist as homodimers and/or heterodimers, on the basis of the observation of dimeric and oligomeric forms of CysLT₁R in Western blots and the punctate appearance of the immunohistochemical signal in peripheral blood leukocytes (Figuerola et al., 2001) or U937 cells (Capra et al., 2005). In human MCs, which can express both receptor subtypes, Mellor et al. (2003) observed that under conditions in which CysLT₁R is blocked, IL-5 generation results only from stimulation with the selective CysLT₂R agonist BAY U9773 and not with cysteinyl LTs, leading them to speculate that this could arise from stimulation of a CysLT₁/CysLT₂ heterodimer at a site inaccessible to interference from MK-571. Finally, Beller et al., (2004b) postulated, on the basis of the magnitude of the attenuation in IgE-dependent, MC-mediated passive cutaneous anaphylaxis in CysLT₁R/CysLT₂R-null mice, that the effect observed in

wild-type littermates was mediated through CysLT₁/CysLT₂ heterodimers. These speculations have been now confirmed by assessment of the formation of a CysLT₁/CysLT₂ heterodimer at the nuclear envelope of human MCs. Negative regulation of CysLT₁R-induced mitogenic signaling responses of MCs by CysLT₂R demonstrates physiologically relevant functions for GPCR heterodimers on primary cells central to inflammation (Jiang et al., 2007). It is noteworthy that recently it has been demonstrated that CysLT₁R formed heterodimers with its counter-receptor CysLT₂R under basal conditions and that LTD₄ triggers reduced dimerization of CysLTRs in intestinal epithelial cells (Parhamifar et al., 2010).

These observations are of potential interest, considering that GPCR oligomerization influences CysLTR pharmacology and function and offers new horizons for the study of important aspects of cysteinyl LT biology and possibly for the development of new drugs (Dalrymple et al., 2008; Kenakin, 2002; Prinster et al., 2005) (see section III.H).

H. Other Receptors Related to CysLT Receptors

Over the years, data were reported in the literature to suggest the existence of additional CysLTR subtypes in human tissues (Brink et al., 2003). This proposal was based on classic pharmacodynamic observations on agonist and antagonist potencies and as well as on receptor pharmacological profiles (Rovati et al., 1997; Bäck, 2002; Norel and Brink, 2004; Rovati and Capra, 2007; Austen et al., 2009).

1. *GPR17*. In an intriguing report Mellor et al. (2001) suggested that in MCs both the CysLT₁R and a yet-unidentified elusive receptor up-regulated by treatment with the proinflammatory cytokine IL-4 were responsive to both cysteinyl LTs and UDP. Pharmacological studies performed with classic CysLT₁R or the dual CysLT₁/CysLT₂R antagonists excluded the possibility that this additional receptor was the CysLT₂R subtype. Subsequently, the hypothesis that the hCysLT₁R was responding to UDP was also excluded (Capra et al., 2005; Woszczek et al., 2010), whereas different CysLT₁R antagonists have been demonstrated to inhibit P2Y receptor signaling (Mamedova et al., 2005; Woszczek et al., 2010).

Screening for orphan GPCRs at an intermediate phylogenetic position between P2Y and CysLT receptor families revealed that the heterologous expression of GPR17 in 1321N1 cells resulted in the generation of an apparently specific and concentration-dependent response to both cysteinyl LTs and extracellular nucleotides (Ciana et al., 2006). In line with previous expression data (Bläsius et al., 1998), both human and rat GPR17 was highly present in brain and in other organs typically undergoing ischemic damage, such as kidney and heart. These data are consistent with the demonstration that both the CysLT₁ and P2Y_{12/13} receptor antagonists (montelukast

and cangrelor, respectively) or in vivo GPR17 receptor knockdown protected against brain damage in the permanent middle cerebral artery occlusion model of ischemic damage in the rat (Ciana et al., 2006). However, GPR17 has been demonstrated to colocalize and dimerize with CysLT₁R on the cell surface of human peripheral blood monocytes and was a negative regulator of the CysLT₁R both in vitro (Maekawa et al., 2009) and in vivo (Maekawa et al., 2010), without inducing a specific response, at least when expressed in a recombinant system. A recent article confirmed that GPR17 is indeed activated by uracil nucleotides (Benned-Jensen and Rosenkilde, 2010), although, at least in isolation, it may not respond to cysteinyl LTs (G. E. Rovati, unpublished observations). In addition, in a different native system (differentiated PC12 cells) knock down of GPR17 by small interfering RNA abolished LTD₄-induced effect on cell viability (Daniele et al., 2010). In this respect, it might be important to note that P2Y₆ receptors also require an intact cysteinyl LT synthesis and signaling system to induce survival and activation of MCs (Jiang et al., 2009). Thus, CysLT₁R and P2Y₆R, which are coexpressed on many cell types of innate immunity, seem to reciprocally amplify one another's function through endogenous ligands. In conclusion, whether GPR17 is really a dualistic receptor (a single protomer responding to two different classes of ligands) or may form heterodimers with a P2Y receptor is a matter certainly deserving further investigation.

2. *Leukotriene E₄ Receptor(s)*. Although LTE₄ is only a weak agonist for the defined CysLT₁R and CysLT₂R, this ligand is the most stable and abundant cysteinyl LT in vivo. However, the literature on LTE₄-induced effects is conflicting, and there seems to be tissue- and model-related differences that remain to be defined. In addition, data from studies in the presence and absence of conversion inhibitors also produced different results (Brink et al., 2003). Early reports indicated greater potency for LTE₄ compared with that for the other cysteinyl LTs in constricting guinea pig trachea in vitro (Lewis et al., 1980; Lee et al., 1984) and comparable activity in eliciting a cutaneous wheal and flare response in humans (Soter et al., 1983). Furthermore, patients with AIA responded with enhanced bronchoconstriction to inhalation of LTE₄ relative to their responses to LTC₄ or histamine (Christie et al., 1993), and inhaled LTE₄ caused more tissue and airway eosinophilia than LTD₄ (Gauvreau et al., 2001). In contrast, LTE₄ failed to activate a CysLTR in human pulmonary vessels (Walch et al., 2002). In 2008, the first report that LTE₄ mediated prostaglandin D₂ production, which was sensitive to the CysLT₁R antagonist MK-571 but resistant to knock down of this receptor, was published (Paruchuri et al., 2008). Furthermore, this effect, induced through COX-2 induction and ERK, p90RSK, and cAMP-regulated-binding protein phosphorylation, was not mediated by LTD₄ but was sensitive to PPAR-γ knockdown, suggesting the

presence of a LTE_4 -selective receptor in human MCs (Paruchuri et al., 2008). Almost simultaneously it was demonstrated that intradermal injection of LTE_4 into the ear of mice deficient in both $\text{CysLT}_1\text{R}/\text{CysLT}_2\text{R}$ elicited a vascular leak that exceeded the response to intradermal injection of LTC_4 or LTD_4 and that this response was inhibited by pretreatment of the mice with PTX or a Rho kinase inhibitor (Maekawa et al., 2008). This putative mouse LTE_4 -specific receptor, however, was not MK-571-sensitive, adding complexity to LTE_4 puzzle (Austen et al., 2009). One last piece of the puzzle has been revealed by the same group on the basis of a study in mice lacking both $\text{CysLT}_1\text{R}/\text{CysLT}_2\text{R}$: the ADP-reactive P2Y_{12} receptor was required for LTE_4 -mediated pulmonary inflammation. Platelet P2Y_{12} receptor expression permitted LTE_4 -induced activation of ERK in CHO cells and allowed chemokine and prostaglandin D_2 production by LAD2 cells, a human MC line. Of interest, competition experiments between radiolabeled ADP and unlabeled LTE_4 in this last system seemed to suggest that P2Y_{12} must complex with another receptor to recognize LTE_4 (Paruchuri et al., 2009). Thus, in the light of the progress on heterodimer pharmacology of GPCRs and their possible physiological significance (Prinster et al., 2005; Gurevich and Gurevich, 2008; Milligan, 2009), the possibility that some of these additional CysLTR subtypes might be the result of the formation of heterodimers with a different pharmacological profile, rather than representing new distinct proteins, should always be considered (see section III.H). In all previous cases, these data add complexity to the already established "cross-talk" between the purinergic and the LT receptor systems (Capra et al., 2005; Jiang et al., 2009), suggesting these as possible additional means by which these two receptor systems interact with each other.

I. New Potential Therapeutic Applications of Leukotriene Receptor Antagonists

1. Allergic Rhinitis. Many of the cells involved in the pathophysiology of AR produce and release cysteinyl LTs, and a connection between the upper airway disease, rhinitis, and lower airway disease, asthma, has been delineated with the aid of important studies indicating that they essentially represent components of a single inflammatory airway disease (Blais, 2005; Thomas, 2006). Molecular and clinical studies also substantiated a role for cysteinyl LTs and their receptors in AR (Peters-Golden and Henderson, 2005; Peters-Golden et al., 2006). Furthermore, beyond the existing connection between AR and asthma, AR and chronic rhinosinusitis seem to be related both epidemiologically and symptomatically. In fact, some studies have demonstrated possible involvement of the cysteinyl LT system in chronic rhinosinusitis also (Arango et al., 2002; Higurashi et al., 2004), and both CysLT_1 and CysLT_2 receptors were expressed in various inflammatory cells of

patients with active seasonal AR (Figueroa et al., 2003) or rhinosinusitis (Sousa et al., 2002) (see section III.A).

Given the shared pathophysiologies and the frequent coexistence, a common therapeutic approach would seem logical (Greenberger, 2003; Stelmach and Cukier, 2006). Indeed, evidence has begun to accumulate in support of the utility of LTRAs in AR (Wilson et al., 2004; Rodrigo and Yañez, 2006) or rhinosinusitis (Grayson and Korenblat, 2007; Scadding et al., 2008).

Montelukast, which significantly reduced daytime nasal, eye and throat symptoms, nighttime symptoms, and symptoms affecting quality of life (QL) in adult patients with seasonal AR (Grainger and Drake-Lee, 2006; Nayak and Langdon, 2007; Bousquet et al., 2009), has also been demonstrated to be safe in children (Bisgaard et al., 2009). Similar results have also been obtained with zafirlukast (Piatti et al., 2003) and pranlukast (Ueda et al., 2003; Okubo and Baba, 2008).

Other studies indicate that LTRAs can alleviate the signs and symptoms of AR when used either as monotherapy (van Adelsberg et al., 2003; Lee et al., 2004b; Ho and Tan, 2007; Wahn and Dass, 2008; Diamant et al., 2009; Cingi and Ozlgedik, 2010) or in combination with an antihistamine in adults (Meltzer et al., 2000; Nayak et al., 2002; Ciprandi et al., 2004; Kurowski et al., 2004; Ciebiada et al., 2006; Lagos and Marshall, 2007; Li et al., 2009), as well as in children (Phan et al., 2009). Results from meta-analyses indicate that antihistamines and LTRAs are equally effective in improving symptoms of AR and QL, but that both drugs are less effective than intranasal corticosteroids (Pullerits et al., 2002; Saengpanich et al., 2003; Di Lorenzo et al., 2004b; Wilson et al., 2004; Rodrigo and Yañez, 2006; Van Hoecke et al., 2007). However, in a retrospective observational study, addition of montelukast to current corticosteroid therapy improved long-term asthma control and resulted in substantial reductions in asthma-related resource use by patients with mild or moderate persistent asthma and concomitant seasonal AR (Borderias et al., 2007), confirming previous results on the efficacy of montelukast in patients with AR and asthma (Nayak, 2004; Philip et al., 2004; Price et al., 2006; Virchow and Bachert, 2006; Storms, 2007). Of interest, systemic medication such as montelukast, as expected, provided better relief for symptoms distant from the nasal cavity, whereas the antihistamine reduced rhinorrhea more than either montelukast or budesonide (Sardana et al., 2010). Both second-generation antihistamines and montelukast have been found to be relatively safe and effective in children also (Phan et al., 2009). Montelukast received approval from the U.S. Food and Drug Administration in January 2003 for the treatment of seasonal AR and in 2005 for the treatment of perennial AR.

2. Aspirin/Nonsteroidal Anti-Inflammatory Drug Intolerance. A variable percentage (2–20%) of adults with asthma exhibit an AIA phenotype (Jawien, 2002), which is the second most frequent untoward allergic reaction to

drugs (de Weck et al., 2006). AIA consists of the precipitation of asthma and rhinitis attacks in the airways or urticaria and angioedema in the skin in response to aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) that inhibit COX-1 (Szczeklik and Stevenson, 2003); selective inhibition of COX-2 does not provoke such responses (Stevenson and Simon, 2001; Gyllfors et al., 2003; Stevenson and Szczeklik, 2006). Within 3 h of ingestion of aspirin or NSAIDs, individuals with AIA develop bronchoconstriction, often accompanied by rhinorrhea, conjunctival irritation, and scarlet flush (Obase et al., 2005). Compared with normal individuals or subjects with aspirin-tolerant asthma, patients with AIA have increased baseline levels of cysteinyl LTs in urine (Christie et al., 1991; Higashi et al., 2004; Micheletto et al., 2006) exhaled air (Antczak et al., 2002), and in saliva and induced sputum (Gaber et al., 2008), levels that are further enhanced by aspirin challenge (Ortolani et al., 1987; Sladek and Szczeklik, 1993; Szczeklik et al., 1996) and that might be derived, at least in part, from MCs (Sladek and Szczeklik, 1993; O'Sullivan et al., 1996; Mita et al., 2001a). Although a definite explanation for this syndrome is not yet available, a large body of evidence supports the possibility that patients with AIA are particularly dependent on the bronchoprotective and anti-inflammatory properties of prostaglandin E₂ (Stevenson and Szczeklik, 2006) and that inhibition of COX-1 in these patients triggers MC activation and release of LTs as well as histamine and tryptase (Picado et al., 1992). In addition to the already discussed high levels of cysteinyl LTs and the localization of CysLT₁R in nasal mucosa and leukocytes of patients with AIA (Sousa et al., 2002), the clinical relevance of the cysteinyl LTs in AIA has been supported by studies demonstrating that patients with AIA respond favorably to clinical treatment with LT modifiers (Dahlén et al., 1998, 2002; Israel, 2000; Mastalerz et al., 2002a,b; Obase et al., 2002; Lee et al., 2004a; Micheletto et al., 2004; Park et al., 2010).

The possible association between *CysLTR1* and *CysLTR2* gene polymorphisms and AIA has already been discussed (see section III.F). *CysLTR1* gene polymorphism, which is often associated with increased CysLT₁R expression, has been found to be associated with AIA in males (Kim et al., 2006b, 2007a). Considering that *CysLTR2* gene polymorphisms, which, on the contrary, seem to affect CysLT₂R mRNA transcription and stability (Shin et al., 2009), have also been found to be associated with AIA, particularly when combined with the LTC₄S polymorphisms –444A>C (Park et al., 2005), one might envisage a protective role for CysLT₂R in AIA. These data seem to support the finding that CysLT₂R, interacting with CysLT₁R, down-modulates cysteinyl LT-dependent responses in MCs (Jiang et al., 2007).

3. Other Atopic Diseases. Beyond asthma and rhinitis, there are other atopic diseases in which cysteinyl LTs are considered to play a role and that normally

affect adults and children with relevant human and economic burden, such as atopic dermatitis (AD) and urticaria. Although the role of cysteinyl LTs in the inflammation of AD is unclear, several reports in the literature, but not all (Veien et al., 2005), detail improvements in patients (adult and children) with moderate to severe AD with the use of LTRAs at the doses generally recommended for asthma treatment (Capra et al., 2006; Leonardi et al., 2007; Broshtilova and Gantcheva, 2010). In support, there is also the evidence that elevated levels of LTE₄ have been found in the urine of patients with AD (Adamek-Guzik et al., 2002; Øymar and Aksnes, 2005). Chronic urticaria (CU) may manifest as an idiopathic reaction or as a reaction to a known cause, such as cold, pressure, food additives, or NSAIDs; however, this does not occur with selective COX-2 inhibitors (Zembowicz et al., 2003). Of interest, the prevalence of aspirin sensitivity among patients with CU is estimated to be between 20 and 30% (Grattan, 2003), and recently the LTC₄S –444A>C polymorphism has been suggested to be a risk factor for aspirin-induced urticaria (Sánchez-Borges et al., 2009). Thus, these patients may be more likely to respond to LTRA therapy (Asero, 2000; Pacor et al., 2001). Indeed, although some authors found LTRAs to be ineffective in CU (Reimers et al., 2002; Di Lorenzo et al., 2004a) or even to induce a paradoxical exacerbation (Minciullo et al., 2004; Tedeschi, 2009), montelukast has been demonstrated to be effective in patients for whom treatment with histamine H₁-receptor antagonists had proved ineffective (Erbagci, 2002; Bagenstose et al., 2004). These data, therefore, suggest that LTRAs may have benefit for patients with conditions not sufficiently controlled with histamine H₁-receptor antagonists (Sanada et al., 2005; Wan, 2009).

4. Cardiovascular Diseases. Biomedical research in the LT field has been markedly polarized to asthma and allergic disorders and has largely overlooked other diseases that are also based on the existence of an inflammatory process with increased vascular permeability and edema, such as CVD (Capra et al., 2007). Although blocking the inflammatory component of any human disease is a long-standing and established concept, the use of LT modifiers (LTRAs and LT synthesis inhibitors) in treating the inflammatory component of CVDs has, surprisingly, been seriously contemplated only in the past few years (Funk, 2005; Peters-Golden and Henderson, 2007; Bäck, 2008b). However, a growing body of evidence suggests a major role for the LTs generated by the 5-LO pathway in the pathogenesis and progression of CVDs (Lötzer et al., 2005; Bäck, 2009a), particularly atherosclerosis, myocardial infarct, stroke, aortic aneurysms, and intimal hyperplasia, as LT signaling is emerging as a crucial component in vascular inflammation (Bäck et al., 2007). Cysteinyl LTs have a unique pharmacological profile, characterized by potent constrictor actions on the microvasculature and thus regulation of blood pressure, enhanced permeability of the

postcapillary venules, reduced coronary blood flow, reduced myocardial contractility, and cardiac output without affecting the heart rate (for review, see Brink et al., 2003 and Capra et al., 2007).

Both CysLTR subtypes are expressed in diseased human arteries (Allen et al., 1998; Spanbroek et al., 2003). However, the role of CysLT₁R in CVDs is rather controversial. Findings suggesting a role for cysteinyl LTs in the extension of ischemic damage and in cardiac dysfunction during reperfusion (Toki et al., 1988; Hock et al., 1992) are evenly balanced by results suggesting that these autacoids have no (Hahn et al., 1992) or little (Ito et al., 1989) contribution to the progression of myocardial ischemia-reperfusion injury. On the other hand, the LTRAs investigated in these studies belong to the first generation of molecules and may have not displayed enough potency to compete with the endogenous ligands, which are likely to be present with very high local bioavailability at sites where inflammatory cell accumulation and myocardial injury take place. In fact, the newer potent and commercially available CysLT₁R antagonist, montelukast, has been found to inhibit atherosclerotic lesion size and intimal hyperplasia (Kaetsu et al., 2007; Jawien et al., 2008) and to reduce vascular reactive oxygen species production, to significantly improve EC function, and to ameliorate atherosclerotic plaque generation in a mouse model *in vivo* (Mueller et al., 2008). Furthermore, in a rabbit carotid balloon injury model, it significantly reduced the neointima, decreased macrophage content, increased SMC content, and inhibited expression of MCP-1 without having influence on plasma lipids, indicating antiatherogenic effects unrelated to plasma lipid modulation (Ge et al., 2009). A randomized controlled trial of placebo versus either montelukast or theophylline in asthmatic individuals reported significantly lower C-reactive protein in montelukast-treated patients (Allayee et al., 2007).

As regards a role for the CysLT₂R in CVD, the early, endothelium-targeted overexpression of the human CysLT₂R in mice aggravates myocardial ischemia-reperfusion injury (Hui et al., 2004), leading to accelerated left ventricular remodeling and impaired cardiac performance (Jiang et al., 2008). Despite expression data suggesting that CysLT₂R is the main isoform of the receptor for cysteinyl LTs in the normal brain (see section III.A), selective CysLT₁R antagonists might have a protective effect in focal cerebral ischemia (Yu et al., 2005a,b; Ciana et al., 2006; Qian et al., 2006), possibly decreasing blood-brain barrier permeability (Biber et al., 2009). However, the dual CysLT₁/CysLT₂ receptor antagonist BAY U9773 has been proved to be more potent and effective than a selective CysLT₁R antagonist in preventing the brain permeability alteration induced by neutrophil activation (Di Gennaro et al., 2004).

The first report indicated that *in vivo* inhibition of GPR17 by either montelukast or antisense technology dramatically reduced ischemic damage in a rat model of

focal cerebral ischemia (Ciana et al., 2006). Subsequently, it was suggested that GPR17 might orchestrate oligodendrocyte maturation after brain or spinal cord injury at a later stage, indicating a role in fostering brain repair (Lecca et al., 2008; Ceruti et al., 2009, 2011). The latter findings were supported by *in vitro* experiments showing that GPR17 activation stimulated the maturation of preoligodendrocytes (Lecca et al., 2008; Fumagalli et al., 2011). In contrast, GPR17 transgenic mice exhibited blocked differentiation of neural progenitor cells into oligodendrocytes and also inhibited terminal differentiation of primary oligodendrocyte precursor cells, supporting GPR17 as a negative regulator of oligodendrocyte differentiation and myelination (Chen et al., 2009b). Fumagalli et al. (2011) recently suggested that one possible explanation for the apparent differences between those studies may be that the overexpression of GPR17 occurred with the CNPase promoter in the latter study (Chen et al., 2009b), inducing GPR17 expression at a rather advanced maturation stage. Nevertheless, GPR17-deficient mice exhibit early onset of central nervous system myelination (Chen et al., 2009b), and the exact role of GPR17 signaling in oligodendrocyte maturation and function remains to be determined. Thus, whether GPR17 or indeed cysteinyl LTs are friends or foes in ischemic brain injury still needs to be established (Bäck, 2008a).

5. CysLT in Other Diseases. A number of observations document that 5-LO and its products may be relevant in different diseases either because of an increase in cysteinyl LT production/CysLTR expression or because the use of LTRAs has proved to be efficacious. For example, cysteinyl LTs have been found in the sputum and urine of patients with cystic fibrosis (CF) (Sampson et al., 1990; Spencer et al., 1992), a disease in which the inflammatory process contributes to progressive lung tissue damage, and their concentrations increase during disease exacerbations together with oxidative stress (Reid et al., 2007). Few studies have been conducted to test the hypothesis that LTRAs have the potential to ameliorate CF lung disease. A pilot study indicated that zafirlukast may benefit adult patients with CF (Conway et al., 2003), whereas montelukast treatment significantly decreased serum (Schmitt-Grohé et al., 2002) and sputum levels of eosinophil cationic protein, IL-8, myeloperoxidase, and increased serum and sputum levels of IL-10 in children (Stelmach et al., 2005). These observations suggest that LTRAs may have measurable anti-inflammatory properties and potential to ameliorate CF lung disease, particularly with long-term use (Schmitt-Grohé et al., 2007). Chronic inflammation also plays a crucial role also in COPD. However, pulmonary inflammation in COPD is, to some extent, different from that in asthma, because other inflammatory cells (i.e., neutrophils, macrophages, and CD8⁺ T lymphocytes) are implicated (Gan et al., 2004). In addition, the profile of exhaled eicosanoids may be different from that previ-

ously reported in asthma: exhaled PGE_2 is selectively increased in COPD, whereas LTE_4 is increased in asthma (Montuschi et al., 2003), but not in COPD (Gaki et al., 2007). There are only a few studies of the clinical effects of LTRAs in COPD. For example, lung function improvement has been observed with zafirlukast in smokers with COPD (Cazzola et al., 2000; Nannini and Flores, 2003). Furthermore, a retrospective study of patients with moderate to severe COPD, reported that montelukast use improved patient's functional scores (shortness of breath, sputum production, wheezing, and nocturnal symptoms), use of drugs (oral and inhaled corticosteroids, inhaled bronchodilators, and supplemental oxygen), number of visits to the emergency department as well as the number and duration of hospitalizations for acute exacerbations (Rubinstein et al., 2004), and QL (Celik et al., 2005). However, further clinical studies are required to judge the real impact of LTRAs in COPD therapy or at least in a subset of patients with COPD (Usery et al., 2008). Given the significant neutrophilic inflammation in COPD, it is likely that LTB_4 has a role in the disease (see also section II.F), and thus BLT antagonists and/or 5-LO/FLAP inhibitors may have greater potential as additional therapy in COPD.

Cysteinyl LTs have been implicated in different liver diseases, such as cholestasis, hepatic inflammation, portal hypertension, and hepatorenal syndrome (Keppler et al., 1988; Farzaneh-Far and Moore, 2003), and their excretion is enhanced in patients with liver cirrhosis and hepatorenal syndrome (Huber et al., 1989). Furthermore, cysteinyl LTs are generated in the liver during the reperfusion period and may contribute to the development of hepatic edema and exert cytotoxicity (Takamatsu et al., 2004). Although inhibition of FLAP abrogated experimental liver injury (Titos et al., 2005) and decreased hepatic inflammation and fibrosis in mice (Horrillo et al., 2007), montelukast was also found to be effective in prevention of liver and intestine injury by reducing apoptosis and oxidative stress in a hepatic ischemia-reperfusion injury model (Daglar et al., 2009) and to improve hepatic fibrosis in cholestatic rats (El-Sweify and Hassanen, 2009).

Finally, the presence of receptors that respond to LTD_4 in human detrusor myocytes (Bouchelouche et al., 2001a) and evidence for increased urinary LTE_4 in patients with interstitial cystitis and detrusor mastocytosis (Bouchelouche et al., 2001b) may suggest a role for cysteinyl LTs as proinflammatory mediators in this disease. Montelukast treatment resulted in significant improvement in urinary frequency and pain (Bouchelouche et al., 2001c), as well in remission of an eosinophilic cystitis (Sterrett et al., 2006), suggesting a role for LTRAs in managing interstitial cystitis.

LTs are elevated in a number of cancers and some pre-clinical cancer models have shown efficacy of early LT synthesis inhibitors (Rioux and Castonguay, 1998; Steele

et al., 1999). In addition, some reports have advanced the concept that GPCRs are mediators of cell growth by demonstrating their potential to activate MAPKs, particularly ERK1/2 (Marinissen and Gutkind, 2001). Several mitogenic pathways might link GPCRs to the nucleus, some of them requiring the capacity of GPCRs to transactivate a growth factor receptor, such as the EGFR (Daub et al., 1996). Indeed, as already discussed in section III.C.1, CysLT_1R activation is able to induce MAPK phosphorylation as well as growth factor receptor transactivation, and, thus, to stimulate proliferation (Wang and Dubois, 2010b). Furthermore, consistent data linking CysLT_1Rs directly to cancer and block of apoptosis are available for epithelial colon cancer cells (Ohd et al., 2003; Nielsen et al., 2005a; Parhamifar et al., 2005; Magnusson et al., 2007, 2010), whereas little information is available on CysLT_1R expression in brain tumors, such as astrocytoma, ganglioglioma, and metastatic adenocarcinoma (Zhang et al., 2004), in prostate cancer (Matsuyama et al., 2007) or in breast cancer (Magnusson et al., 2011). Taken together, these findings encourage the study of pharmacological treatment of selected forms of cancer with the LTRAs already marketed for asthma.

IV. Nomenclature for Leukotriene Receptors

Based on the above-cited studies, the IUPHAR Nomenclature Committee for Leukotriene Receptors concludes that the previously established nomenclature for leukotriene receptors (Brink et al., 2003) remains pertinent. Nevertheless, the present nomenclature may present some limitations, which need to be taken into consideration.

Although 12-HHT is an endogenous ligand for BLT_2R with higher affinity than LTB_4 , the classification of this receptor as the low-affinity receptor for LTB_4 can be motivated by the important amino acid identity with the high-affinity BLT_1R and the close genomic localization of the *LTB4R* and *LTB4R2* genes. However, considering that 12-HHT is produced in platelets more abundantly than LTB_4 , the nomenclature of BLT_2R may be reconsidered in the future.

Second, the interaction between purinergic and leukotriene signaling represents an interesting cross-talk in which leukotrienes may activate purinergic receptors and nucleotides may signal through CysLT receptors. Although there is a phylogenetic relationship between purinergic receptors and leukotriene receptors, the exact interactions between these receptor classes remain to be established. Likewise, classifying the recently deorphanized GPR17 or the P2Y_{12} receptor into the leukotriene receptor class seems to be premature at this time. Finally, although functional studies and in vivo experiments indicate that not all leukotriene-induced responses fit the current receptor classification, the molecular structure of the putative leukotriene receptor(s) is presently unknown.

In conclusion, there is no doubt that leukotriene signaling is complex and may involve several receptor classes. The majority of the known leukotriene-induced effects can be assigned to the currently identified receptor subtypes (Table 1). It is hoped that future studies will extend our current understanding of putative additional leukotriene receptors.

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Wrote or contributed to the writing of the manuscript: Bäck, Dahlén, Drazen, Evans, Serhan, Shimizu, Yokomizo, and Rovati.

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