Update on leukotriene, lipoxin and oxoeicosanoid receptors: IUPHAR Review 7

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1Nomenclature Subcommittee for Leukotriene Receptors, International Union of Basic and Clinical Pharmacology, 2Department of Medicine, Karolinska Institutet, Stockholm, Sweden, 3Department of Cardiology, Karolinska University Hospital, Stockholm, Sweden, 4Meakins-Christie Laboratories, McGill University, Montreal, QC, Canada, 5Harvard Medical School, Brigham and Women’s Hospital, Boston, MA, USA, 6The National Institute of Environmental Medicine, Division of Physiology, Karolinska Institutet, Stockholm, Sweden, 7PharmAkea, San Diego, CA, USA, 8Center for Experimental Therapeutics and Reperfusion Injury, Brigham and Women’s Hospital, Boston, MA, USA, 9National Center for Global Health and Medicine, Shinjyuku, Tokyo, Japan, 10Department of Biochemistry, Juntendo University School of Medicine, Bunkyo-ku, Tokyo, Japan, and 11Laboratory of Molecular Pharmacology, Department of Pharmacological Sciences, University of Milan, Milan, Italy

The endogenous ligands for the LT, lipoxin (LX) and oxoeicosanoid receptors are bioactive products produced by the action of the lipoxygenase family of enzymes. The LT receptors BLT1 and BLT2 are activated by LTB4 and the CysLT1 and CysLT2 receptors are activated by the cysteinyl-LTs, whereas oxoeicosanoids exert their action through the OXE receptor. In contrast to these pro-inflammatory mediators, LXA4 transduces responses associated with the resolution of inflammation through the receptor FPR2/ALX (ALX/FPR2). The aim of the present review is to give a state of the field on these receptors, with focus on recent important findings. For example, BLT1 receptor signalling in cancer and the dual role of the BLT2 receptor in pro- and anti-inflammatory actions have added more complexity to lipid mediator signalling. Furthermore, a cross-talk between the CysLT and P2Y receptor systems has been described, and also the presence of novel receptors for cysteinyl-LTs, such as GPR17 and GPR99. Finally, lipoxygenase metabolites derived from ω-3 essential polyunsaturated acids, the resolvins, activate the receptors GPR32 and ChemR23. In conclusion, the receptors for the lipoxygenase products make up a sophisticated and tightly controlled system of endogenous pro- and anti-inflammatory signalling in physiology and pathology.
Abbreviations
AQP4, aquaporin 4; ATRA, all-trans retinoic acid; AT-RvD3, aspirin-triggered resolvin; BMDM, bone marrow-derived macrophages; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; DC, dendritic cell; EAE, experimental autoimmune encephalitis; GRK, GPCR kinase; OGD, oxygen-glucose deprivation; LX, lipoxin; OIR, oxygen-induced retinopathy; RSV, respiratory syncytial virus; Rv, resolvin

Links to online information in the IUPHAR/BPS Guide to PHARMACOLOGY and the BJP’s ‘Concise Guide to Pharmacology 2013/14

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<th>Targets</th>
<th>Ligands</th>
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<tr>
<td>5-lipoxygenase (5-LOX)</td>
<td>5-(6-chloro-2-hexyl-1H-indol-1-yl)-5-oxo-valeric acid</td>
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<td>12-lipoxygenase (12-LOX)</td>
<td>5-Oxo-ETE</td>
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<td>15-lipoxygenase (15-LOX)</td>
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<td>BLT1 receptor</td>
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<td>acetylsalicylic acid (aspirin)</td>
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<td>CSa receptors</td>
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<td>Chemerin receptor (ChemR23)</td>
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<td>aspirin-triggered lipoxin A (15-epi-LXA, ATL)</td>
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<td>ERK</td>
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<td>GPR32</td>
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<td>p38 MAP kinase</td>
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<td>IFN-γ</td>
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<td>IL-10</td>
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This table lists protein targets and ligands that are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY (Pawson et al., 2014) and the Concise Guide to PHARMACOLOGY 2013/14 (Alexander et al., 2013a,b).
Introduction

The endogenous ligands for the LT, lipoxin (LX) and oxoeicosanoid receptors are bioactive products produced by the action of the lipoxygenase family of enzymes shown in Figure 1 (Brink et al., 2003; Brink et al., 2004; Chiang et al., 2006; Bäck et al., 2011). The metabolism of arachidonic acid by 5-lipoxygenase yields the epoxide intermediate LTA4, which serves as precursor for the LT receptor agonists (Figure 1). Subsequent metabolism through the enzyme LTA4 hydrolase leads to formation of the dihydroxy-LT LTB4, which is the ligand for the BLT receptors (Figure 1). Alternatively, conjugation of LTA4 with glutathione yields the cysteinyl-LTs acting on the two CysLT receptor (CysLTR) subtypes, CysLT1 and CysLT2 (Figure 1). There is also evidence in the literature for additional CysLT receptor subtypes, derived from functional in vitro studies (Lee et al., 1984; Snyder and Krell, 1984; Bäck et al., 2000; Sakata and Bäck, 2002; Walch et al., 2002), radioligand binding (Capra et al., 1998; Ravasi et al., 2000; 2002) and mice lacking both CysLT1 and CysLT2 receptors (Maekawa et al., 2008). LTE4 has, for example, been suggested to signal through P2Y12 receptors in some studies (Nonaka et al., 2005; Paruchuri et al., 2009; Fredman et al., 2010), although not replicated in all settings (Foster et al., 2013). In support of common receptors mediating purinergic and LT signalling, the orphan GPR17 (Figure 1) has been postulated to be activated by both cysteinyl-LTs and nucleotides (Ciana et al., 2006); this will be further discussed below. In addition, recent evidence point to yet another receptor for cysteinyl-LTs, namely, GPR99 (Kanaoka et al., 2013) as indicated in Figure 1.

Oxoeicosanoids are another family of biologically active arachidonic acid derivatives that have been intimately associated with cellular migration (Powell et al., 1995). 5-Oxo-ETE, formed by the oxidation of 5S-HETE by 5-hydroxyeicosanoid dehydrogenase (Figure 1) is a potent chemoattractant for human granulocytes and monocytes by means of the OXE receptor (Brink et al., 2004).

The dual lipoxygenation of arachidonic acid by either the 15- and 5-lipoxygenase or the 5- and 12-lipoxygenase produces eicosanoids known as lipoxins (LXs), as indicated in Figure 1 (Chiang et al., 2006). These eicosanoids are inhibitory or anti-inflammatory mediators, which act as a ‘stop signal’ during inflammatory reactions (Serhan, 2007; Capra et al., 2013) through a receptor with high sequence homology (70%) to the formyl peptide receptors (FPR). However, although a number of peptides activate this receptor, LXA4 is the most potent native endogenous ligand, and the nomenclature recommended for this receptor is FPR2/ALX. The term ALX/FPR2 for the same receptor is suggested when the lipoxin-binding property is of primary concern (Ye et al., 2009).
Besides the 20:4, n-6 fatty acid arachidonic acid, also ω-3 essential polyunsaturated fatty acids, such as eicosapentaenoic acid (EPA; 20:5, n-3) and docosahexaenoic acid (DHA; 22:6, n-3), are metabolized by lipoygenases in human cells (Figure 1). For example, when metabolized by 5-lipoxygenase, EPA generates LTs of the 5-series (e.g. LTB₅, see Figure 1), which are less biologically active and compete with LT binding to the LT receptors, suggesting that lipoygenase metabolites of ω-3 fatty acids may act as inhibitors of inflammation (Stanke-Labesque et al., 2008). Furthermore, EPA and DHA can enter into the lipoxygenase metabolism and lead to the biosynthesis of either E-series (for EPA-derived), or D-series (for DHA-derived) of resolvins (Rv). These ω-3-derived mediators have been characterized as mediators of inflammation resolution by means of signalling through two GPCRs, GPR32 and ChemR23, as will be further discussed below.

The LT, LX and oxoecosanoid receptor cloning, ligand affinity, expression and functional significance have been reviewed in previous IUPHAR reports (Brink et al., 2004; Chiang et al., 2006; Bäck et al., 2011) and are summarized in Tables 1–6. The aim of the present review is to give a state of the field on these receptors, with focus on recent important findings.

BLT receptors

The dihydroxy-LT, LTB₄, stimulates neutrophil chemotaxis and secretion but may also affect immunomodulation through the activation of several leukocyte populations (Bäck et al., 2011; Nakamura and Shimizu, 2011). In addition, receptors for LTB₄ are expressed on non-myeloid cells, such as vascular smooth muscle and endothelial cells (Bäck et al., 2005). Chemotaxis, one of the principal effects of LTB₄, occurs via activation of the BLT₁ receptor subtype (Yokomizo et al., 1997), which is the high-affinity LTB₄ receptor. The open reading frame of the gene encoding a second subtype of BLT receptor was identified during the analysis of the BLT₁ promoter (Yokomizo et al., 2000). This receptor was named BLT₂ and either HEK or CHO cells transfected with BLT₂ cDNA exhibited low affinity to LTB₄ and in addition responded to various other hydroxy fatty acids including 12-epi LTB₄, 12S-HETE and 15S-HETE (Yokomizo et al., 2000). Search for endogenous high-affinity ligands for BLT₂ receptors resulted in the identification of 12-HHT (12(S)-hydroxyheptadeca-5Z, 8E, 10E-trienoic acid), previously known as a by-product of TxA₂ biosynthesis, as a high-affinity BLT₂ receptor ligand (Okuno et al., 2008). Pro-inflammatory LTB₄ signalling through the BLT₁ and BLT₂ receptors has been implicated in several diseases (Bäck et al., 2011; Nakamura and Shimizu, 2011), such as bronchial asthma (Miyanaha et al., 2005; Terawaki et al., 2005), rheumatoid arthritis (Kim et al., 2006; Chou et al., 2010), atherosclerosis (Bäck and Hansson, 2006), abdominal aortic aneurysms (Houard et al., 2009), bone metabolism (Hiiki et al., 2009), multiple sclerosis (Kihara et al., 2010) and cancer (Yokota et al., 2012).

BLT₁ receptor

Structure–function relationships. Of the receptors addressed in the present review, the human BLT₁ receptor is the best characterized in terms of structure–function relationships. Like several rhodopsin family GPCRs, the BLT₁ receptor bears an 8th helix (H8) domain consisting of Val²⁹⁸-Gly-Phe-Val-Ala-Lys-Leu-Leu-Glu-Gly³⁰⁷ (Okuno et al., 2003). Two aromatic residues, Tyr²⁸⁵ and Phe³⁰⁵, may stabilize the inactive form of the BLT₁ receptor by holding H8 at an almost right angle from the C-terminus of the seventh transmembrane region (Okuno et al., 2003). Thus, H8-deficient BLT₁ receptor mutants exhibit a prolonged intracellular signalling after LTB₄ stimulation (Okuno et al., 2003). Hydrophobic amino acid residues in the H8, Val³⁰⁴, Leu³⁰⁴ and Leu³⁰⁵, may act as anchors to the plasma membrane, whereas Thr³¹⁷ located after the H8 is one of the ligand-induced phosphorylation sites mediated by the GPCR kinase GRK6, and involved in BLT₁ receptor inactivation (Gaudreau et al., 2002). Recently, Aratake et al. reported an inhibitory role of the H8 on the LTB₄-elicited internalization of the BLT₁ receptor (Aratake et al., 2012). The human BLT₁ receptor with the mutations of Leu³⁰⁴ and Leu³⁰⁵ in the H8 exhibited an augmentation of LTB₄-induced internalization, whereas the wild-type (WT) receptor exhibited minimal internalization. Furthermore, phosphorylations of 5 Ser and Thr residues between 308 and 319 were important for this enhanced internalization of the mutant BLT₁ receptor. Therefore, the H8 of BLT₁ may repress LTB₄-induced internalization by suppressing excessive phosphorylations.

BLT₁ receptors in inflammation. The generation of BLT₁ receptor-deficient mice confirmed the loss of responsiveness to LTB₄ in BLT₁ receptor null leukocytes (Haribabu et al., 2000; Tager et al., 2000) and the suppression of several inflammation disease models (Bäck et al., 2011). In contrast, transgenic mice overexpressing the human BLT₁ receptor exhibited enhanced responsiveness of leukocytes in acute dermal inflammation (Chiang et al., 1999). Recently, Monteiro et al. reported that macrophages, but not mast cells, are involved in the migration of neutrophils, by generating LTB₄ in haem-induced neutrophilic inflammation, for example, malaria and sickle cell disease (Monteiro et al., 2011). BLT₁ receptor antagonists, CP-105,696 and LY-292476, significantly impaired the haem-induced peritoneal neutrophilia, demonstrating further involvement of the BLT₁ receptor in this inflammatory response (Monteiro et al., 2011).

BLT₁ receptors in cardiovascular disease (CVD). Recurring nocturnal episodes of airway obstruction, known as obstructive sleep apnea syndrome, causes intermittent hypoxia, which is a detrimental stimuli for the cardiovascular system associated with, for example, early atherosclerosis and an increased cardiovascular risk (Stanke-Labesque et al., 2014). Neutrophil granulocytes derived from patients with obstructive sleep apnea exhibit increased LTB₄ production in response to calcium ionophore stimulation, compared with cells derived from healthy subjects (Stanke-Labesque et al., 2012). In addition, expression of LT-synthesizing enzymes in neutrophils correlates with measures of subclinical atherosclerosis and vascular remodelling in these patients (Stanke-Labesque et al., 2012). In support of a role for the LTB₄-BLT₁ pathway in sleep apnea-associated atherosclerosis, mice deficient in both apolipoprotein E and the BLT₁ receptor are protected from the accelerated atherosclerosis observed after subjecting...
apolipoprotein E-deficient mice to intermittent hypoxia in vivo (Li et al., 2011).

Hypertension is associated with increased levels of LTB₄ measured in the saliva (Labat et al., 2013). In addition, cerebral LTB₄ levels are increased in spontaneously hypertensive rats compared with Wistar-Kyoto rats (Waki et al., 2013). In the latter study, microinjection of the BLT₁ receptor antagonist U75302 into the solitary nucleus of spontaneously hypertensive rats lowered arterial pressure, suggesting that LTB₄-BLT₁ receptor inflammatory circuits in the brain stem may be associated with neurogenic hypertension (Waki et al., 2013).

**BLT₁ receptors in rheumatoid arthritis.** Several studies have revealed that BLT₁ receptor-deficient mice are protected from the development of arthritis using different models,
associated with decreased articular neutrophil recruitment (Kim et al., 2006) resulting in reduced production of IL-1 and chemokines in the joint (Chou et al., 2010). In this disease, the recruitment of neutrophils is orchestrated via two pathways, C5a receptor signalling-induced LTB4 release followed by BLT1 receptor activation, and Fcγ receptor signalling-elicited IL-1β release (Sadik et al., 2012).

Table 2

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<th>The BLT2 receptor</th>
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<tbody>
<tr>
<td>Agonists</td>
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<tr>
<td>12-HHT</td>
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<td>CAY10583</td>
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<tr>
<td>LTB4</td>
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<td>LTB4</td>
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<td>12-epi LTB4</td>
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<td>12(S)-HETE</td>
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<td>15(S)-HETE</td>
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<td>Antagonists</td>
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<td>CP195543</td>
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<td>LY255283</td>
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<th>Transduction mechanisms</th>
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<tr>
<td>Transducer</td>
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<td>Gαq; Gα11 family</td>
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<th>Effector/response</th>
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<tr>
<td>Adenylate cyclase inhibition; PLC stimulation</td>
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<th>Examples of receptor distribution</th>
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<tr>
<td>Human spleen, liver, ovary and leukocytes</td>
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<tr>
<td>Human atherosclerotic lesions, human abdominal aortic aneurysms</td>
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<tr>
<td>Synovial tissues derived from patients with rheumatoid arthritis</td>
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<td>Murine small intestine and skin</td>
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<th>Examples of functional assays</th>
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<td>CHO cells transfected with the human BLT2: chemotaxis, increase in intracellular calcium</td>
</tr>
<tr>
<td>MDCK cells transfected with human BLT2: increase in transendothelial resistance.</td>
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<td>Guinea pig lung parenchyma: contraction</td>
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<th>Examples of physiological functions</th>
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<tr>
<td>Chemotaxis</td>
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<td>Angiogenesis</td>
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<th>Examples of pathophysiological functions (confirmed in BLT2-deficient mice)</th>
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<td>Rheumatoid arthritis (in BLT1/BLT2-null mice)</td>
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<tr>
<td>Endothelial function</td>
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<td>Protection against colitis</td>
</tr>
<tr>
<td>Attenuated allergic airway eosinophilia</td>
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<tr>
<td>Tumour</td>
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Full information and references available in the IUPHAR/BPS Guide to PHARMACOLOGY, http://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=268&familyId=35&familyType=GPCR. Currently, LY255283 is used as a BLT2 receptor-specific antagonist, but this compound also inhibits BLT1 in a non-competitive manner. 12-HHT, 12-hydroxyheptadecatrienoic acid.

BLT1 receptors in other diseases. Atopic dermatitis is an inflammatory skin disease. Although LTB4 concentration is elevated in skin lesions of patients with atopic dermatitis, little is known about the role of LTB4 in this disease. Recently, Oyoshi et al. reported an essential role of the LTβ1/BLT1 receptor pathway in neutrophils for allergic skin inflammation (Oyoshi et al., 2012b). In the latter study, allergic skin inflammation was significantly decreased in BLT1-deficient mice, and it was demonstrated that both LTB4 production and BLT1 receptor expression in neutrophils were important for the development of this disease (Oyoshi et al., 2012b).

Recently, the role of the BLT1 receptor signalling in tumour immunology has been investigated. Yokota et al. examined the effect of the BLT1-deficiency on the anti-tumour memory responses elicited by s.c. administration of GM-CSF gene-transduced WEHI3B (WGM) leukaemia cells using BLT1 receptor-deficient mice (Yokota et al., 2012). They found that the BLT1 receptor deficiency resulted in reduced tumour-infiltrating myeloid-derived suppressor cells, increase in mature dendritic cells (DCs) in tumour tissues and
augmentation of CD4+ T-lymphocyte stimulation capacity during GM-CSF-triggered tumour regression, demonstrating that the lack of the LTB4-BLT1 receptor pathway induced long-term anti-tumour memory responses after immunization with WGM leukaemia cells. In another study however, BLT1 receptor-deficient mice exhibited accelerated tumour growth and reduced survival compared with WT mice in a cervical cancer model (Sharma et al., 2013). These findings were associated with a decreased number of CD8+ T-lymphocytes and NK cells in tumours derived from BLT1 receptor-deficient mice, and decreased IFN-γ and IL-2 expression (Sharma et al., 2013). Taken together, those studies

**Table 3**
The CysLT1 receptor

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<tr>
<th>Agonists</th>
<th>Agonists</th>
<th>Affinity</th>
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<tr>
<td>LTD4 (full agonist)</td>
<td>LTD4 (full agonist)</td>
<td>7.3–9.4 (pEC50); 8.1 (pIC50); 8.6–10.6 (pKd)</td>
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<td>LTC4 (full agonist)</td>
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<tr>
<td>LTE4 (partial agonist)</td>
<td>LTE4 (partial agonist)</td>
<td>6.4–7.2 (pEC50); 6.6–6.97 (pIC50)</td>
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<tr>
<td>N-methyl-LTC4 (partial agonist)</td>
<td>N-methyl-LTC4 (partial agonist)</td>
<td>5.7 (pEC50)</td>
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<tr>
<th>Antagonists</th>
<th>Antagonists</th>
<th>Affinity</th>
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<td>Montelukast</td>
<td>8.6 (pKi); 8.3–8.6 (pIC50)</td>
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<td>Zafirlukast</td>
<td>Zafirlukast</td>
<td>8.9 (pKi); 7.7–9.6 (pIC50)</td>
</tr>
<tr>
<td>Pranlukast</td>
<td>Pranlukast</td>
<td>7.1–8.8 (pKi); 8.1–10.0 (pIC50)</td>
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<tr>
<td>Pobilukast</td>
<td>Pobilukast</td>
<td>7.1 (pKi); 7.5–8.2 (pIC50)</td>
</tr>
<tr>
<td>Iralukast</td>
<td>Iralukast</td>
<td>7.8 (pKi)</td>
</tr>
<tr>
<td>Verlukast</td>
<td>Verlukast</td>
<td>8.0 (pIC50)</td>
</tr>
<tr>
<td>BAYu9773</td>
<td>BAYu9773</td>
<td>5.3–6.4 (pIC50)</td>
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Transduction mechanisms

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<th>Transducer</th>
<th>Effector/response</th>
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<tr>
<td>Gq/11 family; Gi/0 family</td>
<td>PI turnover and Ca2+ mobilization; PLC stimulation</td>
</tr>
</tbody>
</table>

Examples of receptor distribution

- Lung, bronchus, bronchiole smooth muscle, airway mucosa
- Nasal polyps
- Peripheral blood leukocytes, macrophages
- Human saphenous vein, human coronary artery smooth muscle cells
- Aortic valves
- Spleen, small intestine and placenta
- Colorectal carcinoma cells

Examples of functional assays

- Several cell types: activation of MAPK
- *X. laevis* melanophores transfected with human CysLT1: pigment dispersion
- *X. laevis* oocyte infected with human CysLT1: Cl current
- HEK293 or COS-7 cells transfected with human CysLT1: [Ca2+]i increase

Examples of physiological functions

- Bronchoconstriction
- Cell proliferation
- Chemotactic activity and migration
- Actin reorganization
- Release of inflammatory mediators and cytokines
- Cell adhesion
- Activation of transcription factors

Examples of pathophysiological functions (confirmed in CysLT1-deficient mice)

- Bleomycin-induced pulmonary inflammation
- Zymosan-induced peritonitis
- Cutaneous anaphylaxis

Full information and references available in the IUPHAR/BPS Guide to PHARMACOLOGY, http://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=269&familyId=35&familyType=GPCR.
suggest that BLT1 receptor signalling on both suppressor and effector cells of the adaptive immune system may be involved in tumour progression and regression.

**BLT2 receptors**
Whereas BLT2 receptor-deficient mice exhibit reduced severity in arthritis models (Mathis et al., 2010), this deletion induces more severe colitis accompanied by the reduced accumulation of IL-13 in the allergic airway (Matsunaga et al., 2013). Taken together, these findings indicate a protective role of the BLT2 receptor in intestinal and airway inflammation.

### Table 4
The CysLT2 receptor

<table>
<thead>
<tr>
<th>Agonists</th>
<th>Affinity</th>
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<tbody>
<tr>
<td>LTC₄ (full agonist)</td>
<td>7.0–8.6 (pEC₅₀); 8.4–8.5 (pIC₅₀); 7.0–10.8 (pKᵩ)</td>
</tr>
<tr>
<td>LTD₄ (full agonist)</td>
<td>6.8–8.6 (pEC₅₀); 7.2–8.2 (pIC₅₀); 7.3–9.4 (pKᵩ)</td>
</tr>
<tr>
<td>LTE₄ (partial agonist)</td>
<td>5.6–7.1 (pEC₅₀); 5.7–6.2 (pIC₅₀); 6.5 (pKᵩ)</td>
</tr>
<tr>
<td>N-methyl-LTC₄ (full agonist)</td>
<td>6.9–8.1 (pEC₅₀)</td>
</tr>
<tr>
<td>BAYu9773 (partial agonist)</td>
<td>7.0–7.2 (pEC₅₀); 6.2–6.4 (pIC₅₀)</td>
</tr>
<tr>
<td>Antagonists</td>
<td>Affinity</td>
</tr>
<tr>
<td>BAYu9773</td>
<td>6.8–7.7 (pA₂); 6.5–6.7 (pKᵩ); 5.3–7.7 (pIC₅₀)</td>
</tr>
<tr>
<td>BayCysLT2</td>
<td>8.3–8.4 (pA₂); 6.6–7.3 (pIC₅₀)</td>
</tr>
<tr>
<td>HAMI3379</td>
<td>7.4–8.4 (pIC₅₀)</td>
</tr>
</tbody>
</table>

Transduction mechanisms

- **Transducer**
  - Gq/11 family; Gi/0 family
- **Effector/response**
  - PLC stimulation; p38 activation
Pharmacological treatment of apolipoprotein E-deficient mice fed a high-fat diet using the BLT2 receptor antagonist LY255283 did not alter atherosclerotic lesion size (Hoyer et al., 2012). However, aortic segments derived from LY255283-treated mice exhibited lower levels of reactive oxygen species (ROS), and increased carbachol-induced endothelium-dependent relaxations compared with untreated mice (Hoyer et al., 2012), suggesting that BLT2 receptor signalling may be involved in endothelial dysfunction. However, it should be taken into consideration that although LY255283 has been used as a BLT2 receptor-specific antagonist, this compound was recently shown to inhibit also the BLT1 receptor in a non-competitive manner (Matsunaga et al., 2013).

Screening a human thymus cDNA to identify BLT2 receptor-interacting proteins recently identified that RanBPM, a member of the Ran-GTPase-binding protein family, which can bind at the C-terminal of the BLT2 receptor in the absence of LTB4, whereas the co-localization of these proteins was abolished in the presence of LTB4 (Wei et al., 2013). RanBPM overexpression attenuated, whereas knockdown promoted, BLT2 receptor-mediated motility and generation of ROS in response to either LTB4 or 12HHT (Wei et al., 2013), suggesting that RanBPM may act as a negative regulator of BLT2 receptor signalling in cell motility. Finally, the BLT2 receptor dissociation from RanBPM was dependent on phosphorylation of BLT2 receptors at Thr355, a site previously identified by the same investigators as critical for LTB4-induced BLT2 receptor-mediated chemotaxis through PI3K-Akt signalling (Wei et al., 2011).

Several recent in vitro studies on BLT2 receptor signalling have focused on different cancer cells. For example, human ovarian and prostate cancer cells express BLT2 receptors coupled to activation of NAD(P)H oxidase-4 (NOX4) and...
subsequent generation of ROS and MMP expression (Lee et al., 2012; Seo et al., 2012), suggesting a BLT2 receptor-dependent pathway in cancer growth, invasiveness and metastasis. In support of the latter, LY255283 inhibits peritoneal metastasis formation 35 days after injection of ovarian cancer cells into athymic mice (Seo et al., 2012).

### CysLT receptors

Ever since the identification of cysteiny1-LT s chemical structure and their association with inflammation (Samuelsson, 1983), the pathophysiological role of cysteiny1-LT s has been mainly focused on their potent bronchoconstrictive effects.

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**Table 6**
The ALX/FPR2 receptor

<table>
<thead>
<tr>
<th>Agonists</th>
<th>Lipid mediators:</th>
<th>Affinity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LXA4 and ATL (full agonist)</td>
<td>12 (pEC50); 8.3–9.3 (pKd)</td>
</tr>
<tr>
<td></td>
<td>RvD1 and AT-RvD1 (full agonist)</td>
<td>11.9 (pEC50)</td>
</tr>
<tr>
<td></td>
<td>Formyl peptides</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PSMe3 (full agonist)</td>
<td>8.7 (pEC50)</td>
</tr>
<tr>
<td></td>
<td>Host-derived non-amyloidogenic peptides</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Annexin A1 (full agonist)</td>
<td>5.8–6.1 (pEC50); 6.5 (pKd)</td>
</tr>
<tr>
<td></td>
<td>SHAAGtide (full agonist)</td>
<td>7.7 (pEC50)</td>
</tr>
<tr>
<td></td>
<td>LL-37 (full agonist)</td>
<td>6.0 (pEC50)</td>
</tr>
<tr>
<td></td>
<td>Host-derived amyloidogenic peptides</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SAA (full agonist)</td>
<td>6.6 (pEC50)</td>
</tr>
<tr>
<td></td>
<td>Peptides identified from library screen</td>
<td></td>
</tr>
<tr>
<td></td>
<td>WKYMVm (full agonist)</td>
<td>9.0–10.1 (pEC50)</td>
</tr>
<tr>
<td>Antagonists</td>
<td>compound 1754-31</td>
<td>7.1 (pIC50)</td>
</tr>
<tr>
<td></td>
<td>WRWRRW</td>
<td>6.6 (pIC50)</td>
</tr>
<tr>
<td></td>
<td>t-Boc-FLFLFL</td>
<td>4.3–6.0 (pIC50)</td>
</tr>
</tbody>
</table>

**Transduction mechanisms**

- **Transducer**: Gi/0 family
- **Effector/response**: PLC, PLA2 and PLD stimulation

**Examples of receptor distribution**

- Peripheral blood leukocytes
- Synovial fibroblasts
- Intestinal epithelial cells
- Lung, kidney, spleen and placenta

**Examples of functional assays**

- PMN, HL-60 cells or CHO cells overexpressing human ALX/FPR2: PLD activation, arachidonic acid release, PSDP increase
- Human macrophages: phagocytosis
- THP-1 cells: calcium mobilization, adherence, chemotaxis
- Human T-cells. ERK activation

**Examples of physiological functions**

- LXA4 and ATL induce anti-inflammatory signals such as reducing CD11b/CD18, expression, blocking ROS production, NF-κB activation, pro-inflammatory cytokines/chemokines.
- LXA4 and ATL give pro-resolving signals, stimulating non-phlogistic monocyte activation (calcium mobilization, adherence and chemotaxis), and macrophage phagocytosis of apoptotic PMN.

**Examples of pathophysiological functions** (confirmed in either Fpr2 or Fpr2/3-deficient mice)

- Mesenteric ischaemia reperfusion
- Carrageenan-induced paw oedema
- K/BxN serum-induced arthritis
- Allergic airway inflammation

Full information and references available in the IUPHAR/BPS Guide to PHARMACOLOGY, [http://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=223&familyId=35&familyType=GPCR](http://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=223&familyId=35&familyType=GPCR).

ATL, aspirin-triggered lipoxin (15-epi-LXA4); SAA, serum amyloid A; SHAAGtide, 18 amino acids from the N-terminal of human CCL23.
and asthma (Drazen, 2003; Capra et al., 2007; Hallstrand and Henderson, 2010; Laidlaw and Boyce, 2012). However, the cloning of the second CysLT receptor, expressed by cardiovascular and cerebral tissues (Brink et al., 2003; Bäck et al., 2011; see also Table 3) has fostered the research for new functions of these lipid mediators in other physiological and pathological conditions, particularly in CVDs. Indeed, CysLT receptor signalling is emerging as a crucial component in vascular inflammation (Bäck, 2007) and an increasing number of data suggest a major role for cysteinyl-LTs in the pathogenesis and progression of several CVDs (Capra et al., 2013), such as atherosclerosis (Bäck and Hansson, 2006), myocardial infarction, stroke (Ingelsson et al., 2012), aortic stenosis (Nagy et al., 2011) and intimal hyperplasia.

**CysLT1 receptor**

CysLT1 receptors in respiratory diseases. The role of CysLT1 receptor signalling in bronchial asthma depends both on the bronchoconstrictive and pro-inflammatory effects of the cysteinyl-LTs (Bäck et al., 2011). Furthermore, bronchial fibroblasts derived from asthmatic subjects express more CysLT1 receptor mRNA compared with bronchial fibroblasts derived from non-asthmatic subjects (Eap et al., 2012). These authors also showed that activation of the asthmatic bronchial fibroblast CysLT1 receptor by cysteinyl-LTs resulted in increased TGF-β1 which in turn increased pro-collagen (Eap et al., 2012). In airway epithelial cells, IL-13 up-regulates the expression of the CysLT1 receptor, which is associated with an increased release of CCL26 (eotaxin-3), a potent eosinophil chemoattractant (Provost et al., 2012). Taken together, those studies suggest that CysLT1 receptor activation on bronchial fibroblasts and epithelial cells further contribute to the cysteinyl-LTs-induced bronchial narrowing and eosinophil recruitment in asthma. Indeed, cells proliferation and bronchial narrowing are hallmarks of chronic asthma. In this regard, an intriguing study (Capra and Rovati, 2014) has recently demonstrated that rosuvastatin, the latest agent of this lipid-lowering class to be introduced on the market, dose-dependently inhibited LTD4-induced human airway smooth muscle cells growth. The letter effect was exerted by means of inhibited prenylation of signalling proteins, most likely small G proteins such as Ras that are activated in a CysLT1 receptor-dependent manner (McMahon et al., 2002; Capra et al., 2003; 2004; Ravasi et al., 2006; Poulin et al., 2011).

Cysteinyl-LTs are increased in children following infection with respiratory syncytial virus (RSV), associated with a potential subsequent development of asthma-like symptoms. In a mouse model of primary and secondary RSV-infection of newborn mice, pretreatment with montelukast, a selective CysLT1 receptor antagonist, decreased RSV-induced airway hyperresponsiveness, airway inflammation and increased IFN-γ production in primary, but not secondary, infected neonate mice (Han et al., 2010).

In addition to asthma, CysLT1 receptor signalling has also been implicated in chronic obstructive pulmonary disease (COPD). Bronchial mucosa samples from patients with COPD exacerbations of increased CysLT1 receptor protein and mRNA expression was demonstrated on inflammatory cells, particularly mast cells and monocytes/macrophages (Zhu et al., 2012).

In line with an activation of the 5-lipoxygenase pathway, urinary LTE4 has been associated with the degree of obstructive sleep apnea in adults (Stanke-Labesque et al., 2009) and children (Shen et al., 2011). In addition, increased cysteinyl-LTs and CysLT1 receptor expression have been shown in tonsillar tissues derived from children with sleep apnea in China (Shen et al., 2012) and in Greece (Tsaoussoglou et al., 2012), suggesting that CysLT1 receptor signalling may contribute to local proliferative and inflammatory pathways within tonsils in paediatric sleep-disordered breathing (Stanke-Labesque et al., 2014). In support of the latter notion, a recent randomized double-blind study of 46 children showed that a 12 week treatment with daily, oral montelukast reduced the severity of obstructive sleep apnea and the underlying adenoidal hypertrophy (Goldbart et al., 2012).

A role for activation of CysLT1 receptors by cysteinyl-LTs in experimental pulmonary fibrosis has been supported by montelukast treatment in several mouse models. In a bleomycin-induced pulmonary fibrosis model in mice, montelukast decreased expression of IL-6, IL-13, IL-10 and TGF-β and attenuated lung fibrosis and hydroxyproline content (Shimbori et al., 2011). In a GATA-3 transcription factor overexpression model, montelukast-treated mice exhibited less airway inflammation in response to ovalbumin challenge, as demonstrated by decreased levels of TGF-β1 cytokines and TGF-β and decreased smooth muscle cell hyperplasia (Ito et al., 2011).

CysLT1 receptor expression increases during T H2 cell differentiation (Parmentier et al., 2012). Human Th2 cells selectively express the CysLT1 receptor, whereas CysLT2 receptor, GPR17 and P2Y12 (other receptors that can respond to cysteinyl-LT; see below) are undetectable. The Th2 cell CysLT1 receptor couples through both Gαq and Gα12 to transduce a chemotactic response. In addition, the dectin-2-cysteiny-1LT pathway is essential for Th2 predominant immunity in mice in response to house dust mite, in part through the CysLT1 receptor (Barrett et al., 2011).

CysLT1 receptors in CVDs. Cysteinyl-LTs are locally produced in coronary atherosclerotic plaques and contribute to vascular inflammation. Although previous studies have shown a dominant CysLT1 receptor expression in vascular smooth muscle cells, lipopolysaccharide stimulation induces CysLT1 receptor expression in human coronary artery vascular smooth muscle cells (Eaton et al., 2012). Interestingly, the CysLT1 receptor exhibited a perinuclear expression in those cells, and its activation was coupled to a predominant nuclear calcium signalling and up-regulation of proatherosclerotic genes such as PAI-2 (Eaton et al., 2012). A nuclear membrane localization of the CysLT1 receptor expression was initially reported in intestinal epithelial cells (Nielsen et al., 2005), and perinuclear expression of the CysLT1 receptor has subsequently been demonstrated in human aortic valve myofibroblasts (Nagy et al., 2011). In the latter cells, the LTC4-induced rise in intracellular calcium was most pronounced in the nuclear and perinuclear region of the cell, associated with mitochondrial permeability transition, changes in cell morphology, increased ROS production and an up-regulation of mRNA encoding bone morphogenic proteins (Nagy et al., 2011), all important pathophysiological processes in the calcification of
the aortic valve observed in patients with calcific aortic stenosis.

The clinical use of the CysLT1 receptor antagonists has allowed testing the hypothesis of their beneficial role in CVD in observational studies. In a pharmacoepidemiological cohort of approximately 7 million subjects, montelukast exposure was associated with a lower risk for recurrent stroke and with a lower risk for recurrent myocardial infarction in male subjects (Ingelsson et al., 2012).

CysLT1 receptors in other diseases. In a mouse model of experimental autoimmune encephalitis (EAE) expression of the CysLT1 receptor mRNA was up-regulated in spleen and lymph node tissue and in the spinal cord, and cysteinyl-LT concentrations in the blood and CSF were higher than in normal mice (Wang et al., 2011). In this EAE mouse model, treatment with CysLT1 receptor-selective antagonists, either montelukast or zafirlukast, reduced CNS CD4 T-lymphocyte influx and demyelination, associated with decreased EAE disease scores.

A role for CysLT1 receptor signalling in various cancers has also been demonstrated. LTD4-induced CysLT1 receptor activation on chronic lymphocytic leukaemia cells and normal B-lymphocytes increases calcium and promote chemotaxis. CysLT1 receptor antagonists induced apoptosis and reduced viability suggesting a potential therapeutic treatment (Drost et al., 2012). In line with the latter suggestion, high CysLT1 and low CysLT2 receptor protein expression in breast cancer tissue is associated with increased cancer-related mortality (Magnusson et al., 2011).

Clinical use of CysLT1 receptor antagonists. It is worth noting here that LT modifiers (including LT receptor antagonists and 5-lipoxygenase inhibitors) are a class of drugs that may be used as an add-on treatment for adult patient with mild persistent asthma not satisfactorily controlled with inhaled glucocorticosteroids, or as alternative treatment particularly in patients suffering from aspirin-sensitive asthma or concomitant allergic rhinitis (Scott and Peters-Golden, 2013). They are generally well tolerated and present few, if any, class-related side effects. LT modifiers can also be safely used in children at all level of asthma severity, particularly against exercise-induced bronchoconstriction, considering virtually the absence of safety concerns (from the Global Strategy for Asthma Management and Prevention, Global Initiative for Asthma (GINA) 2012. Available from http://www.ginasthma.org/). However, LT modifiers are generally less effective than inhaled glucocorticosteroids when used alone as controller (Chauhan and Ducharme, 2012), while long-acting β2-adrenoceptor agonists are modestly superior to LT receptor antagonists in reducing oral corticosteroid-treated exacerbations (Chauhan and Ducharme, 2014).

A number of clinical studies have been published from 2011 to 2013 using the selective CysLT1 receptor antagonists montelukast or pranlukast in asthmatics. For example, montelukast pretreatment decreased hypertonic saline induced bronchoconstriction in asthmatics (Kazani et al., 2011), and provided disease control, similar to that of fluticasone. In actively smoking asthmatics (Price et al., 2013). Furthermore, in an allergen challenge model, pranlukast pretreatment inhibited nasal obstruction and nasal eosinophil cationic protein in allergic Japanese children (Gotoh et al., 2012). Finally, a pilot study indicated that montelukast prevented inflammatory cell responses in patients with persistent rhinitis, with particular emphasis on macrophages and neutrophils (Braido et al., 2012).

LT receptor antagonists have also been studied outside their respiratory indications. A prospective study with zafirlukast in female patients with long-standing mild/severe capsular contracture after surgical procedure for breast prosthesis. The results show a significant decrease in breast compliance values after 6 months of treatment, followed by a substantial increase 1 year after the end of drug intake, suggesting that the control of inflammation is crucial to prevent this multifactorial process (Mazzocchi et al., 2012). Finally, a retrospective study in children with food allergies suggested that montelukast can prevent food-induced adverse allergic reactions such as abdominal pain, which occur during oral immunotherapy (Takahashi et al., 2014).

CysLT2 receptor
CysLT2 receptors in CVDs. A number of studies have reported the involvement of the CysLT2 receptor in the inflammatory process subsequent to brain vascular insults, such as vascular ischaemia or oxygen-glucose deprivation (OGD; Bäck et al., 2011). In a model of focal cerebral ischaemia in the rat, a spatiotemporal up-regulation of the CysLT2 receptor was associated with neuronal and glial cell activation (Zhao et al., 2011). The same authors also demonstrated that the mechanism underlying CysLT2-mediated ischaemic astrocyte injury induced by OGD involves increased expression of the CysLT2 receptor and of the water channel aquaporin 4 (AQP4). The latter was supported by reduced cell injury and AQP4 up-regulation by the CysLT2 receptor antagonist Bay-CysLT2, (also known as CysLT2cpd; Carnini et al., 2011), but not by the highly selective CysLT2 receptor antagonist montelukast (Qi et al., 2011). Furthermore, intracerebroventricular injection of HAMI3379, another even more selective CysLT2 receptor antagonist (Wunder et al., 2010), before focal cerebral ischaemia in rats protects against acute brain injury attenuating the neurological deficits and reducing infarct volume, brain oedema, IgG exudation, neuronal degeneration and neuronal loss (Shi et al., 2012). Of note, the protective effect induced by CysLT2 receptor antagonism was similar to that of pranlukast. In the latter context, it should be considered that pranlukast, zafirlukast and pobilukast have been found to be partially active also at the CysLT2 receptor (Heise et al., 2000; Wunder et al., 2010; Capra et al., 2014).

In further support of neuronal effects of cysteinyl-LTs mainly being CysLT1 receptor-dependent, HAMI3379 inhibited OGD/recovery, as well as LTD4 and N-methyl-LTC4-induced cell injury and neuronal loss in mixed cultures of cortical cells (Zhang et al., 2013). Although no effect of HAMI3379 was observed on OGD/recovery-induced neuronal injury in primary neurons, this antagonist inhibited neuronal loss and necrosis in neuron-microglial co-cultures, indicating that microglial activation may be crucial in this signalling. Similar effects were obtained by CysLT2 receptor knock-down by shRNA, further supporting that these neuronal effects might indeed be CysLT2 receptor-dependent (Zhang et al., 2013).
As mentioned above, the CysLT2 receptor is highly expressed in endothelial cells of some vascular beds, and has been implicated in a variety of cardiovascular functions. BayCysLT2 administered either before or after ischaemia/reperfusion in transgenic mice overexpressing endothelium-specific human CysLT1 receptors attenuated the increased myocardial infarction damage, while this CysLT2 receptor antagonist decreased neutrophil infiltration and leukocyte adhesion molecule (L-selectin) expression (Ni et al., 2011).

CysLT2 receptors in other diseases. Using a loss-of-function murine model (CysLT2R-LacZ), CysLT2 receptor expression has been identified in neurons of the myenteric and submucosal plexus in the small intestine, colonic myenteric plexus, dorsal root ganglia and inferior ganglion of the vagal nerve (Barajas-Espinosa et al., 2011). In this model, LTC4/D4 stimulation of colonic submucosal venules elicited a reduced permeability response in CysLT2 receptor-knockout (CysLT2−/−) mice compared with WT mice, while basal neuronal activity of colonic-projecting nociceptive neurons from dorsal root ganglia showed significantly higher excitability. These data suggest that CysLT2 receptor signalling in the murine colonic ganglia showed significantly higher excitability. These data suggest that CysLT2 receptor signalling in the murine colonic myenteric plexus may be involved in colitis disease progression, controlling inflammation-associated tissue oedema, and in the increased neuronal sensitivity to nociceptive stimuli (Barajas-Espinosa et al., 2011).

Sensitization and challenge using the dust mite Dermatophagoides farinae induces a marked augmentation of eosinophilic pulmonary inflammation, serum IgE, and TNFα, cytokines in CysLT2 receptor-deficient compared with WT mice (Barrett et al., 2012). These observations could be replicated in WT mice sensitized by adoptive transfer of D. farinae-pulsed CysLT2 receptor-deficient bone marrow-derived DCs. Those results, taken together with a previous observation of a counter-regulatory role of CysLT2 with respect to CysLT1 receptor activity by dimerization (Jiang et al., 2007), suggest that the CysLT2 receptor negatively regulates the development of cysteiny1-LT-dependent TNFα pulmonary inflammation by inhibiting both CysLT1 receptor signalling and D. farinae-induced LTC4 synthase-dependent cell surface expression of CysLT1 receptors on DCs (Barrett et al., 2012).

Proliferative diabetic retinopathy is associated with an increased synthesis of LTs (Talahalli et al., 2010) and oxygen-induced retinopathy (OIR) in mice induces CysLT2 receptor up-regulation. CysLT2 receptor knockout mice exhibit decreased vascular leakage and retinal oedema, but, surprisingly, increased tissue damage (vaso-obliteration/vasoproliferation) compared with WT mice. In addition, only PGs and hydroxyeicosatetraenoic acids, but not LTs, were detected in A23187-treated retina preparations (Barajas-Espinosa et al., 2012). Taken together, these data point to a confusing role of CysLT2 receptor signalling in OIR progression that could be interpreted as either beneficial or detrimental to retinal health.

As mentioned above, atopic dermatitis is a chronic, relapsing, inflammatory skin disease characterized by dermal thickening, eosinophil infiltration and increased levels of LTE4 in the urine. Although the role of cysteiny1-LTs in the inflammation associated with atopic dermatitis is unclear, there are reports suggesting improvements in atopic dermatitis with the use of LT receptor antagonists at the doses generally recommended for asthma treatment (see Capra et al., 2006 and Bäck et al., 2011 for more details). Recently, it has been reported that skin thickening and collagen deposition were significantly reduced in ovalbumin-sensitized skin of CysLT2 receptor knockout mice. In addition, LTC4 stimulation caused increased collagen synthesis by human skin fibroblasts, which, in turn, secreted factors that elicited keratinocyte proliferation. These effects were blocked by the dual CysLT1/CysLT2 receptor antagonist BAY u9773 (Oyoshi et al., 2012a).

Since the discovery that activation of CysLT1 receptors could induce MAPK phosphorylation and thus, proliferation, survival and migration in a variety of cells, a number of papers have reported CysLT1 receptor expression in brain tumours, as well as in prostate and breast cancer cells (Bäck et al., 2011). Interestingly, while low expression of CysLT1 and high expression of CysLT2 receptors correlated with high differentiation in epithelial colon cancer cells (Magnusson et al., 2007) and mediate good prognosis in colon (Magnusson et al., 2010) and breast cancer patients (Magnusson et al., 2011), very recently, the same group also demonstrated that all-trans retinoic acid (ATRA) induced CysLT2 receptor and LTC4 synthase mRNA expression (without affecting CysLT1 receptor expression) and differentiation of colorectal cancer cells. This latter effect was inhibited by the CysLT2 receptor-specific antagonist BayCysLT2, suggesting that ATRA can have anti-tumorigenic effects through the cysteiny1-LT pathway (Bengtsson et al., 2013).

OXE receptor

5-Oxo-ETE is formed by the oxidation of 5S-HETE by 5-hydroxyeicosanoid dehydrogenase, a highly selective NADP+-dependent enzyme (Powell et al., 1992) found in most inflammatory cells as well as a variety of structural cells (Grant et al., 2009). Soon after the discovery of this pathway, 5-oxo-ETE was found to be a potent chemoattractant for human neutrophils (Powell et al., 1993) and subsequently also for eosinophils (Powell et al., 1995; Schwenk and Schroder, 1995), monocytes (Sozzani et al., 1996) and basophils (Iikura et al., 2005; Sturm et al., 2005). Consistent with this, it promotes migration of eosinophils through basement membrane and endothelial cells (Dallaire et al., 2003), probably mediated by both its chemoattractant effects as well as by stimulation of MMP-9 secretion (Langlois et al., 2006). 5-Oxo-ETE also induces a variety of other responses in eosinophils and neutrophils, including calcium mobilization, actin polymerization, CD11b expression and shedding of L-selectin (Grant et al., 2009). Although it is less effective in eliciting degranulation and the respiratory burst in resting granulocytes, once these cells have been primed with cytokines, including TNFα, G-CSF or GM-CSF, their responsiveness to 5-oxo-ETE is dramatically increased (OFlaherty et al., 1996a,b; Czech et al., 1997). Interestingly, 5-oxo-ETE induces the release of GM-CSF from monocytes, which has been shown to prolong eosinophil survival (Stamatiou et al., 2004) and could also potentially enhance the responsiveness of leukocytes to this substance.

Biological responses to 5-oxo-ETE are mediated by the OXE receptor, which is encoded by the OXER1 gene (Brink...
et al., 2004). This receptor was identified independently by three groups and was previously known as TG1019 (Hosoi et al., 2002), R527 (Jones et al., 2003) and GPCR48 (Takeda et al., 2002). Consistent with the biological activities of 5-oxo-ETE, OXE receptors are highly expressed in human eosinophils > basophils > neutrophils > macrophages (Hosoi et al., 2002; Ikura et al., 2005) and is also expressed in a variety of cancer cell lines (O’Flaherty et al., 2005; Sundaram and Ghosh, 2006) as well as an adrenocortical cell line (Cooke et al., 2013). Although OXE receptor orthologues exist in a variety of species, including non-human primates, cows, dogs, cats, ferrets and elephants, as well as various fish species, including zebrafish, neither mice nor rats possess an OXE orthologue. The lack of OXER1 in mice has been a significant impediment to progress in our understanding of the pathophysiological role of 5-oxo-ETE and the OXE receptor. In contrast to rodents, zebrafish possess an OXER1 orthologue that plays an important role in leukocyte infiltration (Enyedi et al., 2013). Down-regulation of the zebrafish OXE receptor blocks infiltration of leukocytes in response to both 5-oxo-ETE and injury, suggesting that 5-oxo-ETE is a key regulator of this process.

The OXE receptor is coupled to $G_{i/o}$, as responses to 5-oxo-ETE can be blocked by Pertussis toxin (Powell et al., 1996; Czech et al., 1997; O’Flaherty et al., 2000; Hosoi et al., 2002). Activation of this receptor results in stimulation of a number of second messenger pathways, including PLC, PI3K and ERK and p38 MAPK, as well as inhibition of AC (Norgauer et al., 1996b; Hosoi et al., 2005; Langlois et al., 2009). MAPK-mediated activation of cPLA$_2$ has also been observed (O’Flaherty et al., 1996b). With the exception of inhibition of AC, which is mediated by $a_i$, OXE receptor signalling is mediated by release of the $b_y$ subunits from $G_{a_y}$ (Blattermann et al., 2012). The benzobisthiazole derivative Gue1654 has been reported to selectively block $b_y$-mediated OXE receptor signalling without affecting $a_i$-mediated inhibition of AC (Blattermann et al., 2012).

As a major target of 5-oxo-ETE is the eosinophil, the OXE receptor could play an important role in eosinophilic disorders such as asthma and allergic rhinitis. Consistent with this, intradermal injection of 5-oxo-ETE results in accumulation of eosinophils in human skin, which is more pronounced in asthmatic subjects compared with controls (Muro et al., 2002; Iikura et al., 2002, 2006). The benzobisthiazole derivative Gue1654 has been reported to inhibit eosinophil infiltration in ALX/FPR2 deficient mice (Norling et al., 2013). More recently, RvD1 was identified as another lipid mediator of resolution (Serhan et al., 2002), which could activate human ALX/FPR2 (Krishnamoorthy et al., 2010) recently confirmed in vivo in ALX/FPR2 deficient mice (Norling et al., 2012).

**LXA$_4$ and ALX/FPR2 receptors in vitro**

Functional in vitro studies of cells with endogenous and recombinant ALX/FPR2 expression have generated contradictory results in terms of lipoxin signalling. For example, HEK cells tagged with an ALX/FPR2-$\beta$-arrestin-coupled system have revealed dose-dependent interactions of $\beta$-arrestin and the ALX/FPR2 receptor for both LXA$_4$ (Krishnamoorthy et al., 2010) and 15-epi-LXA$_4$ (Dalli et al., 2013a). In contrast, other investigators reported no $\beta$-arrestin translocation induced by LXA$_4$ in cells expressing the recombinant human ALX/FPR2 receptors (Forsman et al., 2011), while another study using a fusion protein consisting of $\beta$-arrestin-2 and EGFP did not observe any apparent translocation of cytosolic $\beta$-arrestin in the presence of LXA$_4$ (Hanson et al., 2013). Furthermore, whereas the ALX/FPR2 receptor agonist WKYMVM inhibited forskolin-induced cAMP levels in either CHO or HEK293 cells transfected with ALX/FPR2 cDNA, LXA$_4$ and 15-epi-LXA$_4$ were inactive (Hanson et al., 2013; Planaguma et al., 2013). Likewise, WKYMVM, but not LXA$_4$, increased ERK phosphorylation in human neutrophils (Bae et al., 2003) and in HEK293 cells transfected with ALX/FPR2 cDNA (Hanson et al., 2013). However, it is difficult to assess these negative findings with LXA$_4$, whose potent bioactions are now documented by many laboratories, and interpretation with caution may be recommended. First, the use of commercial LXA$_4$ in studies reporting lack of actions for LXA$_4$, without validation of the physical integrity of this molecule just prior to testing in these systems, may be delicate. Second, several of the above studies lacked a positive control for LXA$_4$-induced responses (Hanson et al., 2013) hence making negative observations in ALX/FPR2 receptor expressing cells somewhat difficult to interpret.

There are, in addition, studies supporting differential signalling pathways for different ALX/FPR2 receptor agonists. In ALX/FPR2-transfected CHO cells, WKYMVM, but not LXA$_4$, increased intracellular calcium concentrations. Interestingly,
also peptide ALX/FPR2 receptor agonists exhibited a differential response in the latter cells, which responded to SHAAG and PACAP, but were unresponsive to the glucocorticoid-derived annexin A1 peptide, Ac2–26 (Hanson et al., 2013). In contrast, both LXA₄ and Ac2–26 stimulated receptor internalization in HeLa cells transiently expressing HA-tagged FPR2/ALX receptors (Maderna et al., 2010), suggesting similar signalling pathways for these ligands. Furthermore, a previous study has demonstrated that LXA₄ mediates the Ca²⁺ release-activated Ca²⁺ current Iₑₐₑₑₔ in K562 erythroleukaemia cells (Li et al., 2008). Interestingly, the latter response was mimicked by annexin and the ALX/FPR2 receptor agonist BML-111, and inhibited by interference RNA against ALX/FPR receptors (Li et al., 2008), further supporting specific signalling pathways through ALX/FPR2 receptors for pro-resolution mediators of both protein and lipid structure.

Taken together, the divergent results obtained for different ligands in cells expressing recombinant human ALX/FPR2 receptors may hence be an indication of biased agonism at this receptor. Interestingly, a recent study revealed constitutive dimerization of ALX/FPR2 receptors in transfected HEK293 cells, either as homodimers or heterodimers with FPR1 receptors (Cooray et al., 2013). The homodimer was activated by LXA₄ and Annexin A1 (but not by either SAA or LL-37) and associated with p38/MAPK and heat shock protein 27 signalling leading to IL-10 release. On the other hand, the ALX/FPR2 and FPR1 receptor heterodimers elicited JNK responses. Although different agonists were not tested against the heterodimer, those results provide an initial suggestion that agonist-biased ALX/FPR2 receptor dimerization can distinguish between agonists with distinct downstream signalling (Cooray et al., 2013).

In human airway epithelial cells, LXA₄ induces an increase in intracellular calcium, which is inhibited by the ALX/FPR2 receptor antagonist BOC-2 (Verriere et al., 2012). Furthermore, human lung type II alveolar A549 epithelial cells, which do not express ALX/FPR2 receptors, are unresponsive to LXA₄ (Bonnans et al., 2003). When the latter cells are transfected to constitutively express full-length recombinant human ALX/FPR2 receptors, LXA₄ and 15-epi-LXA₄ suppress IL-6 release induced by acid injury, and IL-8 release induced by either TNF or SAA, whereas the cytokine release induced by those stimuli are unaltered by lipoxin stimulation in untransfected A549 cells (Bonnans et al., 2006; Bozinovski et al., 2012). Although both SAA and lipoxins may signal through ALX/FPR2 receptors, lipoxins induced not only a rightward shift but also a depressed Eₘₐₓ of the SAA-induced IL-8 release, arguing against simple competitive antagonism at a single binding site as a mechanism of inhibition. Applying a Schild analysis to the interaction of lipoxin and SAA yielded a regression slope less than unity and those authors concluded that LXA₄ and 15-epi-LXA₄ may suppress the response to SAA by means of an allosteric type of non-competitive interaction at ALX/FPR2 receptors (Bozinovski et al., 2012). The notion of LXA₄ as an allosteric modulator may however not be selective for only the ALX/FPR2 receptor interactions with LXA₄, since LXA₄ also has recently been reported to allosterically enhance anandamide-induced activation of CB₁ receptors within the brain in an FPR2/ALX receptor-independent manner to mediate protective effect against β-amyloid-induced spatial memory impairment in mice (Pamplona et al., 2012).

The uptake of apoptotic neutrophils by macrophages, known as efferocytosis is one of the cardinal signs of resolution of inflammation (Serhan, 2011). Efferocytosis is stimulated by either LXA₄ or Ac2–26 in bone marrow-derived macrophages (BMDM), whereas BMDMs derived from Fpr2/Fpr3 knockout mice (cf. below) did not increase efferocytosis in response to these agonists (Maderna et al., 2010). Furthermore, NK cells were recently shown to express the ALX/FPR receptor, and LXA₄ significantly increased NK cell-mediated apoptosis of granulocytes, an effect that was inhibited by the ALX/FPR2 receptor antagonist WRW4 (Barnig et al., 2013). Taken together, these results support a role of LXA₄ signalling through ALX/FPR receptors in granulocyte turnover during the resolution of inflammation.

**LXA₄ and ALX/FPR2 receptors in vivo**

The generation of mice with a genetically targeted ALX/FPR receptor orthologue has allowed the exploration of ALX/FPR2 signalling in different disease models. The murine FPR gene family consists of at least eight members as opposed to only three in humans, and both the proteins encoded by the mFpr2 and mFpr3 (mFpr-rs1) genes share the lipoxin binding capacity of the human ALX/FPR2 receptor (Ye et al., 2009; He et al., 2013). There is however also evidence of LXA₄-induced responses in mFpr-rs4-expressing HEK293 cells (Riviére et al., 2009).

In the first report of Fpr2 knockout, the gene cassette and a GFP reporter was inserted in reverse orientation into intron 1 of Fpr2, which prevented transcriptional read-through of the Fpr2 as well as Fpr3 genes (Dufton et al., 2010). Those mice (which were later termed Fpr2/Fpr3 knockout mice) exhibit an increased number of adherent and emigrated leukocytes after mesentery ischaemia-reperfusion, an increased carragenan-induced paw oedema and also an exacerbation and prolongation of K/BxN serum-induced arthritis (Dufton et al., 2010; Brancalone et al., 2013), consistent with the pro-resolution signalling through these murine receptors. Importantly, LXA₄ inhibited cell recruitment into dorsal air pouches inflamed with IL-1β selectively in WT mice but not in Fpr2/Fpr3 receptor knockouts, supporting that LXA₄ exerts its action through the murine Fpr2 and/or Fpr3 receptors in vivo (Dufton et al., 2010).

In the second report, selective Fpr2 receptor deletion was obtained through a recombinase approach (Chen et al., 2010). Those Fpr2 knockout mice exhibit reduced ovalbumin/alum-induced allergic airway inflammation, associated with lower levels of IL-4, IL-5 and IL-13 in BAL and a reduced recruitment of DCs to draining lymph nodes (Chen et al., 2010). Studies of dextran sulphate-induced colitis in this strain revealed that, whereas Fpr2 receptor knockout conferred protection in terms of body weight loss and disease scores in the acute phase, these mice exhibited a delayed healing and increased mortality compared with WT mice after dextran sulphate withdrawal (Chen et al., 2013). In addition, Fpr2 receptor knockout mice displayed increased susceptibility to chronic inflammation-associated colon tumours (Chen et al., 2013) and exacerbated infection and mortality in response to *Listeria monocytogenes* infection. Whether the
ostron and time-dependent phenotypes in terms of exacerbated inflammation and protection in those studies are related to the different disease models or the different Fpr gene targeting remains to be established.

Further in vivo evidence for lipoxin signalling through ALX/FPR2 receptors has been provided using the ALX/FPR2 receptor antagonist BOC-2. In a murine model of pneumonia, LXA4 treatment 24 h after Klebsiella pneumoniae inoculation improved the survival rate of septic mice, an effect that was abolished by the ALX/FPR2 antagonist BOC-2 (Sordi et al., 2013). In addition, LXA4 induces a significant reduction of cerebral infarct size and neurological score when administered before 2 h middle cerebral artery occlusion followed by 24 h reperfusion in rats, an effect that is only partially blocked by the ALX/FPR2 receptor antagonist BOC-2 (Wu et al., 2013), while another study suggested PPARγ may also be involved in the neuroprotective effects of LXA4 in experimental stroke (Sobrado et al., 2009). Finally, using the peptide ALX/FPR2 receptor agonist CGEN-855A, Hecht and co-workers demonstrated inhibition of neutrophil recruitment to inflamed air pouch and protection against myocardial ischaemia-reperfusion injury (Hecht et al., 2009).

Other related receptors

GPR17
The orphan GPR17 (Figure 1), phylogenetically located at an intermediate position between P2Y and CysLT receptors, has been originally postulated to be activated by cysteinyl-LTs, nucleotides and sugar-nucleotides (UDP, UDP-glucose, UDP-galactose), leading to both AC inhibition and intracellular calcium increases (Ciana et al., 2006). Subsequently, a different group confirmed the activation of GPR17 by uracil nucleotides, but was unable to demonstrate activation or binding by cysteinyl-LTs, while demonstrating that both short and long isoforms were constitutively active through Goα (Benned-Jensen and Rosenkilde, 2010). A very recent paper, however, examining the activation of GPR17 for four independent downstream signalling responses in a broad range of cell types, indicated that GPR17 was not activated or internalized by either uracil nucleotides, or cysteinyl-LTs (Qi et al., 2013). Moreover, data from the same report are consistent with GPR17 acting as a negative regulator for CysLT1 receptor-mediated responses, as previously hypothesized by Maekawa and collaborators both in vitro and in vivo (Maekawa et al., 2009; 2010). Thus, the formal pairing of GPR17 as a dual receptor for cysteinyl-LTs and nucleotides is yet to be agreed (Davenport et al., 2013).

Oxoglutarate receptor (formally GPR99)
GPR99, a close relative of GPR91, originally described as an orphan GPCR with homology to the P2Y nucleotide receptor subfamily (Wittenberger et al., 2002), was initially recognized as an oxoglutarate receptor based on its binding of and activation by 2-oxoglutarate (α-ketoglutarate) with potency in the high micromolar range via a Gαi-mediated pathway (He et al., 2004). This pairing has been replicated in a β-arrestin assay (Southern et al., 2013), again with high potency values and eventually named the oxoglutarate receptor in a Receptor Nomenclature and Drug Classification (NC-IUPHAR) committee pairing paper (Davenport et al., 2013). However, recent evidence points to GPR99 as an additional receptor for LTE4. Cells transfected with the human GPR99 exhibit both functional and binding responses to LTE4 with an affinity in the low nanomolar range, while confirming an apparent affinity for oxoglutarate in the high micromolar range. In addition, GPR99 deletion in mice prevents LTE4-induced vascular leakage, but not that induced by LTC4 or LTD4 (Kanaoka et al., 2013). These results, particularly the potencies and affinities values, suggest that GPR99 might have a preference for LTE4 and qualify it as a candidate for the elusive LTE4 receptor, although further investigations on binding and signalling mechanisms and independent confirmations by a different group are necessary to distinguish the preferred endogenous ligands for GPR99.

Chemerin receptor (ChemR23)
ChemR23, an orphan GPCR related to chemokine receptors, was initially described as one of three GPCRs activated by the chemotactic protein chemerin (Wittamer et al., 2003; 2004) and therefore, classified as a pro-inflammatory receptor. However, several subsequent studies using ChemR23 knockout mice in different disease models, such as zymosan-induced peritonitis (Cash et al., 2008), LPS-induced lung injury (Luangsay et al., 2009), viral pneumonia (Bondue et al., 2011b) and cigarette smoke exposure (Demoor et al., 2011) have pointed to an anti-inflammatory role.

Indeed, ChemR23 was in addition identified as a high-affinity RvE1 receptor through screening of the ability of RvE1 to inhibit TNFα-induced NF-κB activation in HEK293 cells after transfection with candidate GPCRs (Arita et al., 2005). Later, RvE1 was also shown to bind to the human BLT1 receptor, albeit with lower affinity (Arita et al., 2007). Radio-ligand studies demonstrated concentration-dependent RvE1 binding to CHO cells expressing ChemR23, but not to mock-transfected CHO cells, associated with Akt phosphorylation also demonstrable in human macrophages during phagocytosis (Ohira et al., 2010). In addition, RvE1 displayed nanomolar potency using a β-arrestin assay in ChemR23-overexpressing cells (Krishnamoorthy et al., 2010). Further studies supported RvE1 signalling also through endogenously expressed ChemR23. For example, RvE1 enhanced phagocytosis in human monocyte-derived macrophages, which was inhibited by a ChemR23 antibody (Ohira et al., 2010). ChemR23 is also expressed on human platelets and RvE1 inhibited ADP-induced platelet activation (Donà et al., 2008). In addition, RvE1 inhibited ADP-induced activation in P2Y12 receptor expressing CHO cells transfected with ChemR23, but not in mock transfected cells, supporting a ChemR23-dependent effect of RvE1 (Fredman et al., 2010). Finally, RvE1 inhibits PDGF-BB-induced proliferation in primary mouse fibroblasts, an effect that is abolished after siRNA-based knock-down of ChemR23 (Qu et al., 2012). RvE1 signalling through ChemR23 has also received support from in vivo studies. Transgenic mice overexpressing ChemR23 under the CD11b promoter exhibit decreased number of leukocytes in peritoneal exudate after zymosan-induced peritonitis, and decreased alveolar bone loss after molar ligation (Gao et al., 2013). In addition, the RvE1-induced leukocyte clearance was...
enhanced in ChemR23 transgenic mice in the peritonitis model (Gao et al., 2013), supporting the notion of ChemR23 as a pro-resolution receptor.

Although some authors have questioned the evidence of RvE1 signalling through ChemR23 (Bondue et al., 2011a; Davenport et al., 2013), only unpublished data were cited in those reviews. These discrepancies, might, at least in part, be explained In light of the recent identified possibility for ChemR23 to form heterodimers with other chemokine receptors (de Poorter et al., 2013).

GPR32

Screening systems to identify receptors for RvD1 revealed two candidates for this lipid mediator, namely ALX/FPR2 and the orphan receptor GPR32 (Krishnamoorthy et al., 2010). This RvD1–GPR32 interaction in human macrophages stimulated miRNA involved in resolution of inflammatory signals (Recchiuti et al., 2011; Recchiuti and Serhan, 2012). Two subsequent studies confirmed this ligand receptor interaction, and extended the observation to show that two other resolvins, RvD5 and RvD3, also activated GPR32 with a similar concentration-response relation (Chiang et al., 2012; Dalli et al., 2013b). Given the relationship between the structures of RvD1, RvD3 and RvD5 and the fact that they are biosynthetically related, this functional mimicry is understandable. However, in an evaluation of 10 500 candidate ligands screened using a β-arrestin assay for 82 GPCRs, RvD1 was not listed to pick out activation of GPR32-expressing cells. Importantly, is should be noted that neither the ligand concentration(s) nor conditions tested were specified in that report and the commercial RvD1 was not validated for structural integrity (Southern et al., 2013) as may be required to fairly assess the potential of these ligand receptor interactions. In further support of biological function associated with the activation of GPR32 by the D-series resolvins, macrophages transfected to express the human GPR32 exhibit an increased phagocytosis of fluorescent Escherichia coli in response to either RvD1 or RvD5 (Chiang et al., 2012). Recently, these observations were extended to show that impedance changes in GPR32-expressing CHO cells were increased upon binding RvD3 and the aspirin-triggered resolvin (AT-RvD3).

Summary and conclusions

Lipid mediators, in particular metabolites of the arachidonic acid cascade, are important signalling molecules for maintenance of homeostasis and development of disease processes. In particular, LTs have proved to be powerful inflammatory and immune regulating mediators in many inflammatory processes, whereas mediators of the lipoxin and resolvin pro-resolution families, activated during host defence, counter-regulate inflammation and promote its resolution. However, as we tried to highlight in this updated report, and despite the many progress in this field of research due to the efforts of a large number of scientists and to the tumultuous progress in technology, there are many issues that still need to be clarified. For example, BLT1 receptor signalling in cancer and the dual role of the BLT2 receptor in pro- and anti-inflammation. Furthermore, the role of cysteiny1-LTs in physiological and pathological conditions other than asthma, particularly in CVDs (Bäck and Hansson, 2006; Bäck, 2007; Nagy et al., 2011; Ingelsson et al., 2012; Capra et al., 2013), or the very interesting issue of the cross-talk between the CysLT and P2Y receptor systems at different levels, agonists/antagonists (Mamedova et al., 2005; Nonaka et al., 2005; Paruchuri et al., 2009; Fredman et al., 2010; Woszczek et al., 2010; Foster et al., 2013) or function/regulation (Capra et al., 2005; Jiang et al., 2009). Likewise, the subcellular localization of functional CysLT1 receptors in the perinuclear region (Nielsen et al., 2005; Nagy et al., 2011; Eaton et al., 2012) opens up for novel signalling pathways for cysteiny1-LTs. Another fascinating notion is the presence of novel receptors for cysteiny1-LTs, such as GPR17 (Ciana et al., 2006; Maekawa et al., 2009; 2010; Benned-Jensen and Rosenkilde, 2010; Qi et al., 2013) or GPR99 (Kanaoka et al., 2013) and resolvin, such as GPR32 (Krishnamoorthy et al., 2010; 2012; Chiang et al., 2012; Southern et al., 2013) and Chem23 (Arita et al., 2005; 2007; Fredman et al., 2010; Bondue et al., 2011a). In conclusion, more comprehensive investigations with in vitro and in vivo models are certainly needed to shed new light on the ever growing roles of this sophisticated and tightly controlled system of endogenous mediators in physiology and pathology.

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Conflicts of interest

None.

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