Review
Allergy Asthma Immunol Res. 2014 July;6(4):288-295.

http://dx.doi.org/10.4168/aair.2014.6.4.288
pISSN 2092-7355 • eISSN 2092-7363

AAIR
Allergy, Asthma & Immunology Research

Cysteinyl Leukotrienes and Their Receptors; Emerging Concepts

Yoshihide Kanaoka[1,2]* Joshua A. Boyce[1,2]

[1]Jeff and Penny Vinik Center for Allergic Disease Research, Boston, MA, United States
[2]Department of Medicine, Harvard Medical School; Division of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Boston, MA, United States

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/3.0/) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

Cysteinyl leukotrienes (cys-LTs) are potent mediators of inflammation derived from arachidonic acid through the 5-lipoxygenase/leukotriene C_4 synthase pathway. The derivation of their chemical structures and identification of their pharmacologic properties predated the cloning of their classical receptors and the development of drugs that modify their synthesis and actions. Recent studies have revealed unanticipated insights into the regulation of cys-LT synthesis, the function of the cys-LTs in innate and adaptive immunity and human disease, and the identification of a new receptor for the cys-LTs. This review highlights these studies and summarizes their potential pathobiologic and therapeutic implications.

Key Words: Leukotrienes; 5-lipoxygenase; asthma; AERD

INTRODUCTION

Leukotrienes are lipid mediators generated from arachidonic acid through the 5-lipoxygenase (5-LO) pathway. They are named for their cells of origin (leukocytes) and the presence of three positionally conserved double bonds (trienes). The 2 classes of leukotrienes, cysteinyl leukotrienes (cys-LTs) and leukotriene B_4 (LTB_4), have broad array of bioactivities and cellular targets. Both 5-LO inhibitors and cys-LT receptor antagonists are useful for the treatment of asthma and rhinitis.[1-3] Recently studies using molecular approaches have demonstrated that cys-LTs possess multiple cell targets and immunologic functions, and act through a receptor system far more complex than previously anticipated. This review highlights these recent studies, and will consider their potential pathobiologic and therapeutic implications.

Regulation of leukotriene synthesis

Leukotriene synthesis is initiated during the activation of leukocytes, when arachidonic acid is liberated from the membrane phospholipids by a cytosolic phospholipase A_2.[4] 5-LO activating protein presents arachidonic acid to 5-LO, which catalyzes the formation of 5-hydroperoxyeicosatetraenoic acid and then the unstable epoxide LTA_4.[5] In mast cells, macrophages, eosinophils, and basophils, LTC_4 synthase (LTC_4S) conjugates LTA_4 to reduced glutathione, forming LTC_4, the parent of the cys-LTs.[6] Once formed, LTC_4 is transported to extracellular space via the ATP-binding cassette (ABC) transporters-1 and-4 and then metabolized to LTD_4 and LTE_4 by γ-glutamyl transpeptidases and dipeptidases, respectively. The rapid extracellular metabolism of LTC_4 and LTD_4 results in short biologic half-lives relative to the stable mediator LTE_4, which is abundant and readily detected in biologic fluids. In neutrophils, LTA_4 is hydrolyzed by a cytosolic LTA_4 hydrolase enzyme to form LTB_4, a dihydroxy leukotriene that is a potent chemoattractant for neutrophils and monocytes.[7]

5-LO activity is substantially upregulated when granulocytes are exposed ex vivo to hematopoietic cytokines such as GM-CSF or (in the case of eosinophils) IL-5.[8-11] In cord blood-derived human mast cells, IL-3 and IL-5 enhance the function of 5-LO by inducing its import from the cytosol to the nucleoplasm, whereas IL-4 potently induces expression and function of LTC_4S.[12] LTC_4S enzymatic function can be inhibited by protein kinase C (PKC)-dependent phosphorylation, which can limit the generation of cys-LTs *ex vivo*.[13] 5-LO activity is suppressed by stimuli that induce cyclic adenosine monophosphate (cAMP) accumulation, leading to serine phosphorylation of 5-LO by cAMP-dependent protein kinase A (PKA).[11] These *in vitro* studies suggest that LT production is tightly regulated by

Correspondence to: Yoshihide Kanaoka, MD, PhD, Brigham and Women's Hospital, 1 Jimmy Fund Way, Smith Building Room 626C, Boston, MA 02115, United States.
Tel: +617-525-1263; fax: +617-525-1310; E-mail: ykanaoka@rics.bwh.harvard.edu
Received: December 3, 2013; Accepted: January 2, 2014
• There are no financial or other issues that might lead to conflict of interest.

© Copyright The Korean Academy of Asthma, Allergy and Clinical Immunology • The Korean Academy of Pediatric Allergy and Respiratory Disease

the microenvironment and intracellular phosphorylation events, with mechanisms that can respectively enhance and limit the expression and function of the critical metabolic enzymes dependent on context.

Cysteinyl leukotriene receptors

Early pharmacologic profiling studies predicted the existence of at least 2 cys-LT receptors in mammalian tissues.[14] The molecular characterization of the classical G protein-coupled receptors (GPCRs) partially reconciled this pharmacology. The type 1 cys-LT receptor, $CysLT_1R$, is a high-affinity receptor for LTD_4 and the target of antagonists (Montelukast, Zafirlukast, and Pranlukast) that are used for the management of asthma. The cloned human $CysLT_1R$ gene encodes a GPCR of 339 amino acids.[15] Human $CysLT_1R$ mRNA is expressed in bronchial smooth muscle and substantially in myeloid cells, such as macrophages and mast cells. The human $CysLT_2R$ is 38% identical to $CysLT_1R$ in amino acid sequence.[16] $CysLT_2R$ binds LTC_4 and LTD_4 with equal affinity, and binds LTD_4 with affinity one-log less than $CysLT_1R$. $CysLT_2R$ is resistant to Montelukast, and is expressed both on cells that also express $CysLT_1R$ (*e.g.*, myeloid cells, smooth muscle), as well as endothelial cells, cardiac Purkinje cells, adrenal medulla, and brain.[16] The incompletely overlapping distribution of the 2 classical receptors for cys-LTs suggests that they have both complementary and distinct functions.

In contrast to their affinities for LTC_4 and LTD_4, the cloned $CysLT_1R$ and $CysLT_2R$ receptors display trivial binding affinity for the stable metabolite LTE_4. Nonetheless, studies of human tracheal explants and guinea pig tracheal rings had predicted the existence of a third cys-LT receptor with a preference for LTE_4.[14,17] LTE_4 also was equipotent to its precursors for inducing wheal and flare responses when injected intradermally into humans.[18] Recently GPR99, previously reported as an oxyglutarate receptor,[19] was identified as a potential LTE_4 receptor.[20] LTE_4 binds and activates GPR99 at low nM range concentrations in transfected cells, and resists blockade by MK571, a prototype $CysLT_1R$ antagonist. The ability of LTE_4 to induce cutaneous vascular permeability in mice depends largely on the presence of GPR99. GPR99 mRNA is expressed strongly by kidney and smooth muscle. Precise definition of its cellular distribution awaits the development of suitable antibody reagents, and its role in allergic inflammation is to be determined.

Regulation of cysteinyl leukotriene receptor function

As is the case for the cys-LT synthesis, cellular responsiveness to cys-LTs can be modulated both by exogenous stimuli and intracellular phosphorylation events. IL-4 and IL-13 upregulate the expression and function of $CysLT_1R$ by human peripheral blood monocytes and monocyte-derived macrophages.[21] IL-13, but not IL-4, upregulates $CysLT_2R$ expression as well in human monocytes.[22] IL-13 and transforming growth factor beta induce $CysLT_1R$ expression by human bronchial smooth muscle cells.[23] $CysLT_1R$ can be inducibly expressed by mouse T cells stimulated through the T cell receptor.[24] $CysLT_1R$ signaling is also controlled by PKA[25] - or PKC[26] -dependent phosphorylation and desensitization. PKC mediates ligand-induced internalization of $CysLT_1R$ following stimulation with LTD_4.[27] PKC activation by members of the purinergic (P2Y) family of GPCRs, which are homologous to the cys-LT receptors, can induce heterologous, PKC-dependent phosphorylation and desensitization of $CysLT_1R$ without causing its internalization.[26] Since nucleotides, the natural ligands for P2Y receptors, are released in large quantities during acute inflammatory responses,[28] signaling through the cognate P2Y receptors may limit potentially deleterious effects of $CysLT_1R$ signaling in cells that express both classes of receptors (Figure). Moreover, the overlap in the cytokines (IL-4) and protein kinases (PKA, PKC) that respectively enhance and suppress the functions of the synthetic and receptor systems suggest that cys-LT production may be regulated in parallel with end-organ responsiveness.

$CysLT_1R$ functions can also be regulated by direct physical interactions with other GPCRs. $CysLT_1R$ and $CysLT_2R$ heterodimerize in cultured human mast cells.[29] The presence of $CysLT_2R$ limits the levels of membrane expression of $CysLT_1R$, and dampens the capacity of $CysLT_1R$ to induce phosphorylation of extracellular signal regulated kinase and proliferation in this cell type. GPR17, a GPCR homologous to $CysLT_1R$ and $CysLT_2R$,[30] was originally "deorphanized" as a dual-specific receptor for cys-LTs and uracil nucleotides.[31] However, we and others could not reproduce GPR17 activation by either ligand type in various assay systems.[30,32,33] Instead, GPR17 functions as a negative regulator of LTD_4-mediated $CysLT_1R$ activation, and markedly reduces binding of LTD_4 when the two receptors are co-expressed in cell lines.[30] Accordingly, mice lacking GPR17 (*Gpr17 −/−* mice) showed markedly enhanced $CysLT_1R$-dependent tis-

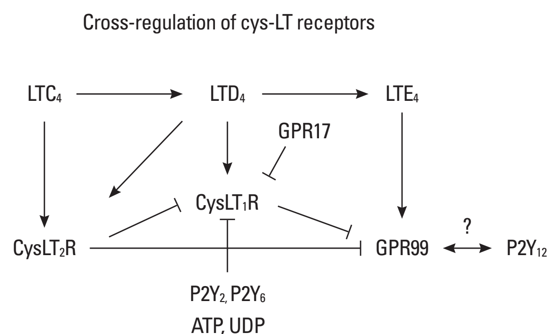

Figure. Cross-regulation of the cysteinyl leukotriene receptors. $CysLT_1R$ function is inhibited both by direct physical interactions with $CysLT_2R$ or GPR17, and by heterologous, PKC-dependent phosphorylation by P2Y receptors. The lack of both $CysLT_1R$ and $CysLT_2R$ amplifies cutaneous responses to LTE_4, suggesting that both classical receptors cross-regulate GPR99. The requirement for $P2Y_{12}$ receptors for the ability of LTE_4 to amplify pulmonary eosinophilia could reflect an interaction with GPR99.

sue edema induced by IgE-dependent passive cutaneous anaphylaxis.[30] Thus, at least two GPCRs ($CysLT_2R$ and GPR17) dampen $CysLT_1R$ function by direct physical interactions. The fact that both direct and indirect mechanisms can limit signaling through $CysLT_1R$ (Figure) implies that such limitation is critical for homeostasis of immune and inflammatory responses.

Cys-LTs in human allergic disease

Asthma and rhinitis

Based on their potencies as airway smooth muscle spasmogens and inducers of vascular leak, cys-LTs were considered potential pathogenetic mediators of asthma and rhinitis decades before the cloning of the cys-LT receptors. When administered by inhalation to asthmatic and nonasthmatic human subjects, both LTC_4 and LTD_4 induced bronchoconstriction at doses several log-fold lower than histamine.[34-36] LTE_4 was a weaker bronchoconstrictor than LTC_4 and LTD_4, but was ~1-log-fold more potent in inducing bronchoconstriction in asthmatic subjects relative to nonasthmatic controls.[37] Additionally, when delivered by inhalation, LTE_4 caused the accumulation of eosinophils and basophils in the bronchial submucosa of mild asthmatic subjects, whereas LTD_4 did not.[38] In retrospect, these findings not only implied that end-organ reactivity to LTE_4 is specifically enhanced in asthma, but also suggested the existence of distinct receptors with a preference for binding and activation by LTE_4.

Cys-LT production increases substantially in association with allergic inflammation and asthma, likely reflecting the activation of mast cells and eosinophils in the lesional tissues.[39] Unfractionated leukocytes from subjects with asthma generate several fold higher levels of both LTB_4 and LTC_4 than do leukocytes from the blood of nonasthmatic controls in response to stimulation with calcium ionophore.[40] Urinary levels of LTE_4 increase during spontaneous asthma exacerbations,[41] and correlate with decline in FEV1.[42] Treatments with either zileuton, a 5-LO inhibitor,[43] or with antagonists of $CysLT_1R$[44] each reduce the frequency of asthma exacerbations. Intravenous Montelukast increases peak expiratory flow rates in adult asthmatic subjects presenting to the emergency department with airflow obstruction compared with placebo.[45] These findings suggest that cys-LTs contribute substantially to exacerbations of asthma. $CysLT_1R$ antagonists also attenuate the magnitude of decline in FEV_1 in response to allergen challenge.[46] Cys-LT-generating enzymes are expressed by eosinophils, monocytes, and mast cells in nasal biopsies from subjects with allergic rhinitis,[39] and $CysLT_1R$ and $CysLT_2R$ localize to both hematopoietic and non-hematopoietic cell types in the nasal tissue.[39,47] Additionally, $CysLT_1R$ is expressed by human Th2 cells in peripheral blood from atopic subjects.[48] Montelukast, alone or in combination with an H_1 histamine receptor antagonist, is superior to placebo for reducing nasal congestion in the treatment of seasonal allergic rhinitis.[3] The effects of $CysLT_1R$ antagonists on rhinitis may reflect the actions of the cys-LTs on the vasculature as well as resident inflammatory cells.

AERD

AERD is characterized by adult onset asthma, severe rhinosinusitis with nasal polyps, and idiosyncratic respiratory reactions to aspirin and other nonselective inhibitors of cyclooxygenase (COX).[49] Baseline levels of urinary LTE_4 in subjects with AERD exceed the levels seen in aspirin tolerant asthmatic controls by several fold, and increase further and markedly in response to provocative challenge with aspirin.[50] The administration of either Zileuton or $CysLT_1R$ antagonists attenuates the severity of aspirin-induced bronchoconstriction in AERD.[51] Both classes of drugs were also superior to placebo for improving sinonasal function.[2,52] Thus, cys-LTs are involved in both the upper and lower respiratory tract pathology typical of AERD.

Eosinophils are the most abundant effector cell in bronchial and nasal biopsies from patients with AERD, and show over-expression of LTC_4S protein relative to eosinophils in biopsies from aspirin tolerant controls.[53,54] Platelets, which lack 5-LO, also express LTC_4S and can convert granulocyte-derived LTA_4 to LTC_4 through a transcellular mechanism.[55] In the blood and nasal polyps from patients with AERD, eosinophils, monocytes, and neutrophils display markedly increased numbers of adherent platelets compared to samples from aspirin tolerant controls.[56] These adherent platelets contribute as much as 60% of the LTC_4S activity associated with peripheral blood granulocytes obtained from subjects with AERD, and the percentages of blood granulocytes that are platelet-adherent correlated strongly with the levels of urinary LTE_4.[56] Mast cell activation accompanies the responses to aspirin challenge in AERD,[57] and the administration of mast cell stabilizing cromone drugs blocks the rise in urinary LTE_4 that accompanies reactions.[58] Collectively, these studies suggest that the dysregulation of cys-LT production in AERD reflects several cell types. Recently developed models of AERD in mice (see below) may more precisely define the cellular and molecular mechanisms responsible for dysregulated cys-LT production in AERD.

In addition to dysregulated cys-LT generation, subjects with AERD show enhanced end-organ reactivity to cys-LTs. Compared with aspirin tolerant asthmatic controls, individuals with AERD demonstrate bronchoconstriction in response to inhaled LTE_4[59] and LTD_4[60] at significantly lower doses. The numbers and percentages of $CysLT_1R$-positive mast cells, eosinophils, and monocytes in nasal biopsies from patients with AERD exceed those observed in the tissues of aspirin-tolerant asthmatic controls.[47,61] $CysLT_1R$ expression on hematopoietic cells decreases following desensitization to aspirin,[61] a procedure that attenuates bronchial reactivity to LTE_4.[62] The numbers and distributions of $CysLT_2R$-positive cells do not differ between aspirin tolerant asthmatics and subjects with AERD. Interestingly, bronchial reactivity to inhaled LTD_4 in AERD or aspirin tolerant

Allergy Asthma Immunol Res. 2014 July;6(4):288-295. http://dx.doi.org/10.4168/aair.2014.6.4.288

asthma does not correlate with the numbers of $CysLT_1R$- or $CysLT_2R$- expressing cells in bronchial biopsies.[60] It is tempting to speculate that non-classical receptors, such as GPR99, may account for a component of the end organ responsiveness to cys-LTs (particularly to LTE_4) observed in AERD.

Understanding functions of the cys-LTs and their receptors in mice

The development of mice lacking LTC4S (*Ltc4s–/–*), $CysLT_1R$ (*Cysltr1–/–*), $CysLT_2R$ (*Cysltr2–/–*), and both receptors (*Cysltr1/Cysltr2–/–*) has permitted in-depth studies of the role of cys-LTs in immune and inflammatory responses. These studies have revealed complex and, in some instances, unanticipated functions for cys-LTs and their receptors in a variety of biologic responses detailed below.

Vascular leak

In a mast cell and IgE-dependent model of passive cutaneous anaphylaxis, *Ltc4s–/–* mice displayed reductions in ear skin swelling of ~50% compared to wild-type (WT) mice .[63] Intraperitoneal injections of zymosan, a yeast cell wall glycan that elicits LTC_4 generation from macrophages, induced vascular leak that was reduced in both the *Ltc4s–/–* and *Cysltr1–/–* strains by ~50% compared with WT controls.[63,64] The responses of *Cysltr2–/–* mice were equivalent to those of WT controls. Thus, $CysLT_1R$ plays a key role in mediating vascular leak in models where cys-LTs are generated in response to antigen- or pathogen-dependent stimuli.

To determine whether additional cys-LT receptors participated in vascular leak, we subjected *Cysltr1/Cysltr2–/–* mice to direct intracutaneous challenges with cys-LTs. Surprisingly, LTC_4 and LTD_4 induced tissue edema in *Cysltr1/Cysltr2–/–* mice that was comparable to WT mice, and LTE_4 induced marked tissue edema in this strain, with 64-fold enhanced sensitivity to LTE_4 over the WT controls. This enhanced response to LTE_4 was inhibited by pretreatment of the mice with pertussis toxin and a Rho kinase inhibitor, suggesting that it was mediated by a previously unrecognized G protein-coupled cys-LT receptor with a preference to LTE_4.[65] Given that GPR99 bound LTE_4 in transfected cells, we generated *Gpr99–/–* and *Gpr99/Cysltr1/Cysltr2–/–* mice for comparison with WT and *Cysltr1/Cysltr2–/–* mice. GPR99 deletion from the *Cysltr1/Cysltr2–/–* mice eliminated the vascular leak in response to the cys-LT ligands, indicating that GPR99 is likely to be a true cys-LT receptor. Furthermore, the *Gpr99–/–* mice showed a dose-dependent loss of LTE_4-mediated vascular permeability, but not to LTC_4 or LTD4, suggesting a preference of GPR99 for LTE_4.[20]

Th2 Immunity

Lung Th2 immunity to the house dust mite *Dermatophagoides farinae (Df)* requires stimulation of the myeloid C-type lectin receptor, Dectin-2.[66,67] Based on a protocol of sensitization of naive WT mice by means of adoptive transfer of *Df*-pulsed dendritic cells (DCs), Th2 responses to *Df* require the expressions of LTC_4S and $CysLT_1R$ by DCs. Interestingly, both *Cysltr2–/–* mice and *Gpr17–/–* mice showed markedly augmented eosinophilic pulmonary inflammation, serum IgE, and Th2 cytokine generation in response to *Df* sensitization and challenge compared to WT controls.[18] *Df*-pulsed DCs derived from *Cysltr2–/–* mice and *Gpr17–/–* mice induce an enhanced pulmonary eosinophilic and Th2 immune response in WT mice when compared with WT DCs. The enhanced response induced by *Gpr17–/–* DCs was eliminated by introduction of the *Cysltr1–/–* allele,[68] whereas the introduction of the *Ltc4s–/–* allele eliminated the potentiation of Th2 immunity induced by transfer of *Cysltr2–/–* DCs.[69] Thus, constitutive downregulation of $CysLT_1R$ function by GPR17 and $CysLT_2R$ may be critical to maintain homeostasis during the induction of Th2 immunity, at least to allergens (and potentially microbes) that bear ligands for Dectin-2.

Activation of innate lymphoid cells

Type 2 innate lymphoid cells (ILC2) are innate lymphocytes that release large quantities of IL-5 and IL-13 when activated by cytokines, such as IL-33, IL-25, or thymic stromal lymphopoietin (TSLP), derived from epithelial cells.[70] A recent study implicated the cys-LTs in the activation of ILC2 cells. Intrapulmonary challenge of mice with an extract from the mold *Alternaria alternata* strongly induced the generation of cys-LTs in the lung, and the recruitment and activation of ILC2.[71] ILC2 expressed $CysLT_1R$, and responded to stimulation in vitro and in vivo with LTD_4 by proliferating and releasing cytokines. Interestingly, while both LTD_4 and IL-33 caused lung ILC2 to generate IL-5 and IL-13, only LTD_4 caused them to generate IL-4. Ex vivo stimulation of lung ILC2 with either LTD_4 or LTE_4 caused the production of IL-5. While the IL-5 production in response to LTD_4 could be blocked by Montelukast, LTE_4-induced IL-5 production was resistant to Montelukast. This study suggests that cys-LTs can contribute to Th2 immunity through direct actions at ILC2. These effects reflect cys-LT actions both classical and nonclassical receptors that can induce effector cytokine production.

Platelet-dependent pulmonary eosinophilia

Platelets are essential for the development of pulmonary eosinophilia and airway remodeling in mouse models of ovalbumin (OVA) sensitization and challenge.[72,73] Activated platelets express P-selectin, which permits their adherence to leukocytes and primes leukocytes for directed migration via integrins. Mouse and human platelets express both $CysLT_1R$ and $CysLT_2R$,[74,75] as well as the $P2Y_{12}$ receptor, a homologue of the cys-LT receptors that binds ADP. Stimulation of mouse platelets with LTC_4 strongly induces their expression of P-selectin in an entirely $CysLT_2R$-dependent manner, while LTD_4 or LTE_4 are inactive. Intratracheal administration of LTC_4, but not LTD_4, mark-

edly amplifies the recruitment of eosinophils to the airways of sensitized mice challenged with low-dose OVA. This amplification requires platelets, and is attenuated in *Cysltr2–/–* mice, suggesting a direct stimulatory effect of LTC_4 on platelet-associated $CysLT_2R$ in the lung vasculature.

Although LTE_4 fails to directly activate mouse or human platelets *in vitro*,[75,76] intratracheal administration of LTE_4, like that of LTC_4, potentiates OVA-induced eosinophilia in a platelet-dependent manner in WT mice.[76] In this model, LTE_4 is fully active in *Cysltr1/Cysltr2–/–* mice, suggesting that it acts at a non-classical cys-LT receptor. Both the effects of LTE_4 (*in vivo*) and of LTC_4 (*in vivo* and *in vitro*) depend exquisitely on the $P2Y_{12}$ receptor.[75,76] A computer modeling study predicted that $P2Y_{12}$ receptors might recognize LTE_4 as a surrogate ligand,[77] and LTE_4 elicits calcium flux[77] and phosphorylation of extracellular signal regulated kinase[76] in transfected cells over-expressing human $P2Y_{12}$ receptors. Nonetheless, radiolabeled LTE_4 does not directly bind to microsomal membranes from $P2Y_{12}$ receptor-expressing transfectants. It is presently unknown whether the involvement of $P2Y_{12}$ in LTE_4-dependent signaling responses and airway inflammation reflects a direct interaction between $P2Y_{12}$ receptors and a bona fide LTE_4 receptor, such as GPR99. The therapeutic potential of drugs that block $P2Y_{12}$ receptors in asthma or AERD is unexplored.

AERD-like models

Although several cellular abnormalities in eicosanoid synthesis and receptor function have been described in AERD,[49] the lack of a valid model of the disease has restrained progress in defining the key pathogenetic steps. Hirata *et al.* generated a transgenic mouse strain over expressing LTC_4S and examined the phenotype in OVA-induced pulmonary inflammation with or without treatment with a COX inhibitor, sulpyrine.[78] OVA-challenged LTC_4S-transgenic mice, but not similarly treated WT mice, demonstrated a significant increase in airway resistance by sulpyrine treatment. This is associated with increases in LTC_4 and LTB_4 in bronchoalveolar lavage (BAL) fluid in sulpyrine-treated OVA-challenged transgenic mice. Importantly, the increase in airway resistance was inhibited by Pranlukast, a $CysLT_1R$ antagonist. This study demonstrates that the pathognomonic feature of aspirin-induced bronchoconstriction can be reproduced in a mouse model, and suggests that the overexpression of LTC_4S described in tissues from patients with AERD[53] has a potentially causal role.

Prostaglandin E_2 (PGE_2) controls cys-LT generation by activating PKA and inducing phosphorylation of 5-LO.[79] Tissue inflammation is typically associated with increased PGE_2 production, reflecting the co-expression of 2 inducible enzymes; COX-2 (a largely aspirin-resistant enzyme) and microsomal PGE_2 synthase-1 (mPGES-1), which isomerizes COX-2-derived PGH_2 to PGE_2.[80] Nasal polyps from subjects with AERD contain less PGE_2 than nasal polyps from aspirin tolerant controls,[81] possibly relating to epigenetic modifications of COX-2[82] and/or mPGES-1 expression.[83] Mice lacking mPGES-1 (*Ptges–/–*) cannot upregulate PGE_2 production with inflammation, and display a remarkably AERD-like phenotype when subjected to a model of *Df*-induced pulmonary disease. Compared with WT controls, *Ptges–/–* mice show increased eosinophilic inflammation and levels of cys-LTs in the BAL fluid. Challenge with inhaled lysine aspirin causes marked increases in airway resistance, robust release of cys-LTs, and pulmonary mast cell activation in the *Ptges–/–* strain, but not in WT controls.[84] Aspirin challenge profoundly depletes lung PGE_2 in the *Ptges–/–* mice, but not in the WT controls, suggesting that the mPGES-1 is needed to maintain PGE_2 levels when COX-1 is inhibited. *Ptges–/–* mice also show increased numbers of platelet-adherent granulocytes in both the peripheral blood and lungs compared with WT controls. Importantly, cys-LT production, mast cell activation, and the changes in airway resistance were blocked by depletion of platelets or blockade of the TP receptor for thromboxane A_2. This model may be useful in defining the potential pathogenetic role of GPR99, $CysLT_2R$, and $P2Y_{12}$ receptors in AERD, as well as unraveling the complex interplay between cys-LTs, platelets, and mast cells that lead to the physiologic response to aspirin challenges.

CONCLUSIONS

While the drugs capable of inhibiting cys-LT formation and blocking $CysLT_1R$ are useful, it is clear that the cys-LT system is far more complex than initially appreciated. The involvement of the cys-LTs in the induction of Th2 immunity and the effector phase of the immune response suggests additional potential applications for currently available pharmacologic agents. However, the recognition that cys-LTs act through at least three receptors and the resistance of 2 of these ($CysLT_2R$ and GPR99) to the blockade by currently available drugs presents both challenges and opportunities for further therapeutic development. The availability of a broad array of valid animal models should facilitate progress in this area, while continuing to reveal unanticipated biological functions for the cys-LTs and their receptors.

ACKNOWLEDGMENTS

This work was supported by NIH grants AI078908, AI095219, AT002782, AI082369, HL111113, HL117945, and HL36110, and by the Vinik Family.

REFERENCES

1. Israel E, Rubin P, Kemp JP, Grossman J, Pierson W, Siegel SC, Tinkelman D, Murray JJ, Busse W, Segal AT, Fish J, Kaiser HB, Ledford D, Wenzel S, Rosenthal R, Cohn J, Lanni C, Pearlman H, Karahalios

P, Drazen JM. The effect of inhibition of 5-lipoxygenase by zileuton in mild-to-moderate asthma. Ann Intern Med 1993;119:1059-66.
2. Dahlén B, Nizankowska E, Szczeklik A, Zetterström O, Bochenek G, Kumlin M, Mastalerz L, Pinis G, Swanson LJ, Boodhoo TI, Wright S, Dubé LM, Dahlén SE. Benefits from adding the 5-lipoxygenase inhibitor zileuton to conventional therapy in aspirin-intolerant asthmatics. Am J Respir Crit Care Med 1998;157:1187-94.
3. Meltzer EO, Malmstrom K, Lu S, Prenner BM, Wei LX, Weinstein SF, Wolfe JD, Reiss TF. Concomitant montelukast and loratadine as treatment for seasonal allergic rhinitis: a randomized, placebo-controlled clinical trial. J Allergy Clin Immunol 2000;105:917-22.
4. Clark JD, Milona N, Knopf JL. Purification of a 110-kilodalton cytosolic phospholipase A2 from the human monocytic cell line U937. Proc Natl Acad Sci U S A 1990;87:7708-12.
5. Reid GK, Kargman S, Vickers PJ, Mancini JA, Léveillé C, Ethier D, Miller DK, Gillard JW, Dixon RA, Evans JF. Correlation between expression of 5-lipoxygenase-activating protein, 5-lipoxygenase, and cellular leukotriene synthesis. J Biol Chem 1990;265:19818-23.
6. Lam BK, Penrose JF, Freeman GJ, Austen KF. Expression cloning of a cDNA for human leukotriene C4 synthase, an integral membrane protein conjugating reduced glutathione to leukotriene A4. Proc Natl Acad Sci U S A 1994;91:7663-7.
7. Palmantier R, Rocheleau H, Laviolette M, Mancini J, Borgeat P. Characteristics of leukotriene biosynthesis by human granulocytes in presence of plasma. Biochim Biophys Acta 1998;1389:187-96.
8. Cowburn AS, Holgate ST, Sampson AP. IL-5 increases expression of 5-lipoxygenase-activating protein and translocates 5-lipoxygenase to the nucleus in human blood eosinophils. J Immunol 1999;163:456-65.
9. Boyce JA, Lam BK, Penrose JF, Friend DS, Parsons S, Owen WF, Austen KF. Expression of LTC4 synthase during the development of eosinophils in vitro from cord blood progenitors. Blood 1996;88:4338-47.
10. Owen WF Jr, Rothenberg ME, Silberstein DS, Gasson JC, Stevens RL, Austen KF, Soberman RJ. Regulation of human eosinophil viability, density, and function by granulocyte/macrophage colony-stimulating factor in the presence of 3T3 fibroblasts. J Exp Med 1987;166:129-41.
11. Flamand N, Surette ME, Picard S, Bourgoin S, Borgeat P. Cyclic AMP-mediated inhibition of 5-lipoxygenase translocation and leukotriene biosynthesis in human neutrophils. Mol Pharmacol 2002;62:250-6.
12. Hsieh FH, Lam BK, Penrose JF, Austen KF, Boyce JA. T helper cell type 2 cytokines coordinately regulate immunoglobulin E-dependent cysteinyl leukotriene production by human cord blood-derived mast cells: profound induction of leukotriene C(4) synthase expression by interleukin 4. J Exp Med 2001;193:123-33.
13. Ali A, Ford-Hutchinson AW, Nicholson DW. Activation of protein kinase C down-regulates leukotriene C4 synthase activity and attenuates cysteinyl leukotriene production in an eosinophilic substrain of HL-60 cells. J Immunol 1994;153:776-88.
14. Lee TH, Austen KF, Corey EJ, Drazen JM. Leukotriene E4-induced airway hyperresponsiveness of guinea pig tracheal smooth muscle to histamine and evidence for three separate sulfidopeptide leukotriene receptors. Proc Natl Acad Sci U S A 1984;81:4922-5.
15. Lynch KR, O'Neill GP, Liu Q, Im DS, Sawyer N, Metters KM, Coulombe N, Abramovitz M, Figueroa DJ, Zeng Z, Connolly BM, Bai C, Austin CP, Chateauneuf A, Stocco R, Greig GM, Kargman S, Hooks SB, Hosfield E, Williams DL Jr, Ford-Hutchinson AW, Caskey CT, Evans JF. Characterization of the human cysteinyl leukotriene CysLT1 receptor. Nature 1999;399:789-93.
16. Heise CE, O'Dowd BF, Figueroa DJ, Sawyer N, Nguyen T, Im DS, Stocco R, Bellefeuille JN, Abramovitz M, Cheng R, Williams DL Jr, Zeng Z, Liu Q, Ma L, Clements MK, Coulombe N, Liu Y, Austin CP, George SR, O'Neill GP, Metters KM, Lynch KR, Evans JF. Characterization of the human cysteinyl leukotriene 2 receptor. J Biol Chem 2000;275:30531-6.
17. Jacques CA, Spur BW, Johnson M, Lee TH. The mechanism of LTE4-induced histamine hyperresponsiveness in guinea-pig tracheal and human bronchial smooth muscle, in vitro. Br J Pharmacol 1991;104:859-66.
18. Soter NA, Lewis RA, Corey EJ, Austen KF. Local effects of synthetic leukotrienes (LTC4, LTD4, LTE4, and LTB4) in human skin. J Invest Dermatol 1983;80:115-9.
19. He W, Miao FJ, Lin DC, Schwandner RT, Wang Z, Gao J, Chen JL, Tian H, Ling L. Citric acid cycle intermediates as ligands for orphan G-protein-coupled receptors. Nature 2004;429:188-93.
20. Kanaoka Y, Maekawa A, Austen KF. Identification of GPR99 protein as a potential third cysteinyl leukotriene receptor with a preference for leukotriene E4 ligand. J Biol Chem 2013;288:10967-72.
21. Thivierge M, Staňková J, Rola-Pleszczynski M. IL-13 and IL-4 up-regulate cysteinyl leukotriene 1 receptor expression in human monocytes and macrophages. J Immunol 2001;167:2855-60.
22. Shirasaki H, Seki N, Fujita M, Kikuchi M, Kanaizumi E, Watanabe K, Himi T. Agonist- and T(H)2 cytokine-induced up-regulation of cysteinyl leukotriene receptor messenger RNA in human monocytes. Ann Allergy Asthma Immunol 2007;99:340-7.
23. Espinosa K, Bossé Y, Stankova J, Rola-Pleszczynski M. CysLT1 receptor upregulation by TGF-beta and IL-13 is associated with bronchial smooth muscle cell proliferation in response to LTD4. J Allergy Clin Immunol 2003;111:1032-40.
24. Prinz I, Gregoire C, Mollenkopf H, Aguado E, Wang Y, Malissen M, Kaufmann SH, Malissen B. The type 1 cysteinyl leukotriene receptor triggers calcium influx and chemotaxis in mouse alpha beta- and gamma delta effector T cells. J Immunol 2005;175:713-9.
25. Capra V, Accomazzo MR, Gardoni F, Barbieri S, Rovati GE. A role for inflammatory mediators in heterologous desensitization of CysLT1 receptor in human monocytes. J Lipid Res 2010;51:1075-84.
26. Capra V, Ravasi S, Accomazzo MR, Citro S, Grimoldi M, Abbracchio MP, Rovati GE. CysLT1 receptor is a target for extracellular nucleotide-induced heterologous desensitization: a possible feedback mechanism in inflammation. J Cell Sci 2005;118:5625-36.
27. Naik S, Billington CK, Pascual RM, Deshpande DA, Stefano FP, Kohout TA, Eckman DM, Benovic JL, Penn RB. Regulation of cysteinyl leukotriene type 1 receptor internalization and signaling. J Biol Chem 2005;280:8722-32.
28. Idzko M, Hammad H, van Nimwegen M, Kool M, Willart MA, Muskens F, Hoogsteden HC, Luttmann W, Ferrari D, Di Virgilio F, Virchow JC Jr, Lambrecht BN. Extracellular ATP triggers and maintains asthmatic airway inflammation by activating dendritic cells. Nat Med 2007;13:913-9.
29. Jiang Y, Borrelli LA, Kanaoka Y, Bacskai BJ, Boyce JA. CysLT2 receptors interact with CysLT1 receptors and down-modulate cysteinyl leukotriene dependent mitogenic responses of mast cells. Blood 2007;110:3263-70.
30. Maekawa A, Balestrieri B, Austen KF, Kanaoka Y. GPR17 is a negative regulator of the cysteinyl leukotriene 1 receptor response to

leukotriene D4. Proc Natl Acad Sci U S A 2009;106:11685-90.
31. Ciana P, Fumagalli M, Trincavelli ML, Verderio C, Rosa P, Lecca D, Ferrario S, Parravicini C, Capra V, Gelosa P, Guerrini U, Belcredito S, Cimino M, Sironi L, Tremoli E, Rovati GE, Martini C, Abbracchio MP. The orphan receptor GPR17 identified as a new dual uracil nucleotides/cysteinyl-leukotrienes receptor. EMBO J 2006;25:4615-27.
32. Qi AD, Harden TK, Nicholas RA. Is GPR17 a P2Y/leukotriene receptor? examination of uracil nucleotides, nucleotide sugars, and cysteinyl leukotrienes as agonists of GPR17. J Pharmacol Exp Ther 2013;347:38-46.
33. Hennen S, Wang H, Peters L, Merten N, Simon K, Spinrath A, Blättermann S, Akkari R, Schrage R, Schröder R, Schulz D, Vermeiren C, Zimmermann K, Kehraus S, Drewke C, Pfeifer A, König GM, Mohr K, Gillard M, Müller CE, Lu QR, Gomeza J, Kostenis E. Decoding signaling and function of the orphan G protein-coupled receptor GPR17 with a small-molecule agonist. Sci Signal 2013;6:ra93.
34. Drazen JM. Comparative contractile responses to sulfidopeptide leukotrienes in normal and asthmatic human subjects. Ann N Y Acad Sci 1988;524:289-97.
35. Weiss JW, Drazen JM, Coles N, McFadden ER Jr, Weller PF, Corey EJ, Lewis RA, Austen KF. Bronchoconstrictor effects of leukotriene C in humans. Science 1982;216:196-8.
36. Weiss JW, Drazen JM, McFadden ER Jr, Weller PF, Corey EJ, Lewis RA, Austen KF. Comparative bronchoconstrictor effects of histamine, leukotriene C, and leukotriene D in normal human volunteers. Trans Assoc Am Physicians 1982;95:30-5.
37. Davidson AB, Lee TH, Scanlon PD, Solway J, McFadden ER Jr, Ingram RH Jr, Corey EJ, Austen KF, Drazen JM. Bronchoconstrictor effects of leukotriene E4 in normal and asthmatic subjects. Am Rev Respir Dis 1987;135:333-7.
38. Gauvreau GM, Parameswaran KN, Watson RM, O'Byrne PM. Inhaled leukotriene E(4), but not leukotriene D(4), increased airway inflammatory cells in subjects with atopic asthma. Am J Respir Crit Care Med 2001;164:1495-500.
39. Figueroa DJ, Borish L, Baramki D, Philip G, Austin CP, Evans JF. Expression of cysteinyl leukotriene synthetic and signalling proteins in inflammatory cells in active seasonal allergic rhinitis. Clin Exp Allergy 2003;33:1380-8.
40. Sampson AP, Thomas RU, Costello JF, Piper PJ. Enhanced leukotriene synthesis in leukocytes of atopic and asthmatic subjects. Br J Clin Pharmacol 1992;33:423-30.
41. Drazen JM, O'Brien J, Sparrow D, Weiss ST, Martins MA, Israel E, Fanta CH. Recovery of leukotriene E4 from the urine of patients with airway obstruction. Am Rev Respir Dis 1992;146:104-8.
42. Green SA, Malice MP, Tanaka W, Tozzi CA, Reiss TF. Increase in urinary leukotriene LTE4 levels in acute asthma: correlation with airflow limitation. Thorax 2004;59:100-4.
43. Liu MC, Dubé LM, Lancaster J. Acute and chronic effects of a 5-lipoxygenase inhibitor in asthma: a 6-month randomized multicenter trial. Zileuton Study Group. J Allergy Clin Immunol 1996;98:859-71.
44. Israel E, Chervinsky PS, Friedman B, Van Bavel J, Skalky CS, Ghannam AF, Bird SR, Edelman JM. Effects of montelukast and beclomethasone on airway function and asthma control. J Allergy Clin Immunol 2002;110:847-54.
45. Camargo CA Jr, Gurner DM, Smithline HA, Chapela R, Fabbri LM, Green SA, Malice MP, Legrand C, Dass SB, Knorr BA, Reiss TF. A randomized placebo-controlled study of intravenous montelukast for the treatment of acute asthma. J Allergy Clin Immunol 2010;125:374-80.
46. Hamilton A, Faiferman I, Stober P, Watson RM, O'Byrne PM. Pranlukast, a cysteinyl leukotriene receptor antagonist, attenuates allergen-induced early- and late-phase bronchoconstriction and airway hyperresponsiveness in asthmatic subjects. J Allergy Clin Immunol 1998;102:177-83.
47. Corrigan C, Mallett K, Ying S, Roberts D, Parikh A, Scadding G, Lee T. Expression of the cysteinyl leukotriene receptors cysLT(1) and cysLT(2) in aspirin-sensitive and aspirin-tolerant chronic rhinosinusitis. J Allergy Clin Immunol 2005;115:316-22.
48. Parmentier CN, Fuerst E, McDonald J, Bowen H, Lee TH, Pease JE, Woszczek G, Cousins DJ. Human T(H)2 cells respond to cysteinyl leukotrienes through selective expression of cysteinyl leukotriene receptor 1. J Allergy Clin Immunol 2012;129:1136-42.
49. Laidlaw TM, Boyce JA. Pathogenesis of aspirin-exacerbated respiratory disease and reactions. Immunol Allergy Clin North Am 2013;33:195-210.
50. Christie PE, Tagari P, Ford-Hutchinson AW, Charlesson S, Chee P, Arm JP, Lee TH. Urinary leukotriene E4 concentrations increase after aspirin challenge in aspirin-sensitive asthmatic subjects. Am Rev Respir Dis 1991;143:1025-9.
51. White A, Ludington E, Mehra P, Stevenson DD, Simon RA. Effect of leukotriene modifier drugs on the safety of oral aspirin challenges. Ann Allergy Asthma Immunol 2006;97:688-93.
52. Dahlén SE, Malmström K, Nizankowska E, Dahlén B, Kuna P, Kowalski M, Lumry WR, Picado C, Stevenson DD, Bousquet J, Pauwels R, Holgate ST, Shahane A, Zhang J, Reiss TF, Szczeklik A. Improvement of aspirin-intolerant asthma by montelukast, a leukotriene antagonist: a randomized, double-blind, placebo-controlled trial. Am J Respir Crit Care Med 2002;165:9-14.
53. Cowburn AS, Sladek K, Soja J, Adamek L, Nizankowska E, Szczeklik A, Lam BK, Penrose JF, Austen FK, Holgate ST, Sampson AP. Overexpression of leukotriene C4 synthase in bronchial biopsies from patients with aspirin-intolerant asthma. J Clin Invest 1998;101:834-46.
54. Adamjee J, Suh YJ, Park HS, Choi JH, Penrose JF, Lam BK, Austen KF, Cazaly AM, Wilson SJ, Sampson AP. Expression of 5-lipoxygenase and cyclooxygenase pathway enzymes in nasal polyps of patients with aspirin-intolerant asthma. J Pathol 2006;209:392-9.
55. Maclouf J, Murphy RC, Henson PM. Transcellular biosynthesis of sulfidopeptide leukotrienes during receptor-mediated stimulation of human neutrophil/platelet mixtures. Blood 1990;76:1838-44.
56. Laidlaw TM, Kidder MS, Bhattacharyya N, Xing W, Shen S, Milne GL, Castells MC, Chhay H, Boyce JA. Cysteinyl leukotriene overproduction in aspirin-exacerbated respiratory disease is driven by platelet-adherent leukocytes. Blood 2012;119:3790-8.
57. Fischer AR, Rosenberg MA, Lilly CM, Callery JC, Rubin P, Cohn J, White MV, Igarashi Y, Kaliner MA, Drazen JM, Israel E. Direct evidence for a role of the mast cell in the nasal response to aspirin in aspirin-sensitive asthma. J Allergy Clin Immunol 1994;94:1046-56.
58. Yoshida S, Amayasu H, Sakamoto H, Onuma K, Shoji T, Nakagawa H, Tajima T. Cromolyn sodium prevents bronchoconstriction and urinary LTE4 excretion in aspirin-induced asthma. Ann Allergy Asthma Immunol 1998;80:171-6.
59. Christie PE, Schmitz-Schumann M, Spur BW, Lee TH. Airway responsiveness to leukotriene C4 (LTC4), leukotriene E4 (LTE4) and histamine in aspirin-sensitive asthmatic subjects. Eur Respir J

1993;6:1468-73.
60. Corrigan CJ, Napoli RL, Meng Q, Fang C, Wu H, Tochiki K, Reay V, Lee TH, Ying S. Reduced expression of the prostaglandin E2 receptor E-prostanoid 2 on bronchial mucosal leukocytes in patients with aspirin-sensitive asthma. J Allergy Clin Immunol 2012;129:1636-46.
61. Sousa AR, Parikh A, Scadding G, Corrigan CJ, Lee TH. Leukotriene-receptor expression on nasal mucosal inflammatory cells in aspirin-sensitive rhinosinusitis. N Engl J Med 2002;347:1493-9.
62. Arm JP, O'Hickey SP, Spur BW, Lee TH. Airway responsiveness to histamine and leukotriene E4 in subjects with aspirin-induced asthma. Am Rev Respir Dis 1989;140:148-53.
63. Kanaoka Y, Maekawa A, Penrose JF, Austen KF, Lam BK. Attenuated zymosan-induced peritoneal vascular permeability and IgE-dependent passive cutaneous anaphylaxis in mice lacking leukotriene C4 synthase. J Biol Chem 2001;276:22608-13.
64. Maekawa A, Austen KF, Kanaoka Y. Targeted gene disruption reveals the role of cysteinyl leukotriene 1 receptor in the enhanced vascular permeability of mice undergoing acute inflammatory responses. J Biol Chem 2002;277:20820-4.
65. Maekawa A, Kanaoka Y, Xing W, Austen KF. Functional recognition of a distinct receptor preferential for leukotriene E4 in mice lacking the cysteinyl leukotriene 1 and 2 receptors. Proc Natl Acad Sci U S A 2008;105:16695-700.
66. Barrett NA, Rahman OM, Fernandez JM, Parsons MW, Xing W, Austen KF, Kanaoka Y. Dectin-2 mediates Th2 immunity through the generation of cysteinyl leukotrienes. J Exp Med 2011;208:593-604.
67. Barrett NA, Maekawa A, Rahman OM, Austen KF, Kanaoka Y. Dectin-2 recognition of house dust mite triggers cysteinyl leukotriene generation by dendritic cells. J Immunol 2009;182:1119-28.
68. Maekawa A, Xing W, Austen KF, Kanaoka Y. GPR17 regulates immune pulmonary inflammation induced by house dust mites. J Immunol 2010;185:1846-54.
69. Barrett NA, Fernandez JM, Maekawa A, Xing W, Li L, Parsons MW, Austen KF, Kanaoka Y. Cysteinyl leukotriene 2 receptor on dendritic cells negatively regulates ligand-dependent allergic pulmonary inflammation. J Immunol 2012;189:4556-65.
70. Spits H, Artis D, Colonna M, Diefenbach A, Di Santo JP, Eberl G, Koyasu S, Locksley RM, McKenzie AN, Mebius RE, Powrie F, Vivier E. Innate lymphoid cells--a proposal for uniform nomenclature. Nat Rev Immunol 2013;13:145-9.
71. Doherty TA, Khorram N, Lund S, Mehta AK, Croft M, Broide DH. Lung type 2 innate lymphoid cells express cysteinyl leukotriene receptor 1, which regulates TH2 cytokine production. J Allergy Clin Immunol 2013;132:205-13.
72. Pitchford SC, Momi S, Giannini S, Casali L, Spina D, Page CP, Gresele P. Platelet P-selectin is required for pulmonary eosinophil and lymphocyte recruitment in a murine model of allergic inflammation. Blood 2005;105:2074-81.
73. Pitchford SC, Riffo-Vasquez Y, Sousa A, Momi S, Gresele P, Spina D, Page CP. Platelets are necessary for airway wall remodeling in a murine model of chronic allergic inflammation. Blood 2004;103:639-47.
74. Hasegawa S, Ichiyama T, Hashimoto K, Suzuki Y, Hirano R, Fukano R, Furukawa S. Functional expression of cysteinyl leukotriene receptors on human platelets. Platelets 2010;21:253-9.
75. Cummings HE, Liu T, Feng C, Laidlaw TM, Conley PB, Kanaoka Y, Boyce JA. Cutting edge: Leukotriene C4 activates mouse platelets in plasma exclusively through the type 2 cysteinyl leukotriene receptor. J Immunol 2013;191:5807-10.
76. Paruchuri S, Tashimo H, Feng C, Maekawa A, Xing W, Jiang Y, Kanaoka Y, Conley P, Boyce JA. Leukotriene E4-induced pulmonary inflammation is mediated by the P2Y12 receptor. J Exp Med 2009;206:2543-55.
77. Nonaka Y, Hiramoto T, Fujita N. Identification of endogenous surrogate ligands for human P2Y12 receptors by in silico and in vitro methods. Biochem Biophys Res Commun 2005;337:281-8.
78. Hirata H, Arima M, Fukushima Y, Honda K, Sugiyama K, Tokuhisa T, Fukuda T. Over-expression of the LTC4 synthase gene in mice reproduces human aspirin-induced asthma. Clin Exp Allergy 2011;41:1133-42.
79. Luo M, Jones SM, Flamand N, Aronoff DM, Peters-Golden M, Brock TG. Phosphorylation by protein kinase a inhibits nuclear import of 5-lipoxygenase. J Biol Chem 2005;280:40609-16.
80. Murakami M, Naraba H, Tanioka T, Semmyo N, Nakatani Y, Kojima F, Ikeda T, Fueki M, Ueno A, Oh S, Kudo I. Regulation of prostaglandin E2 biosynthesis by inducible membrane-associated prostaglandin E2 synthase that acts in concert with cyclooxygenase-2. J Biol Chem 2000;275:32783-92.
81. Yoshimura T, Yoshikawa M, Otori N, Haruna S, Moriyama H. Correlation between the prostaglandin D(2)/E(2) ratio in nasal polyps and the recalcitrant pathophysiology of chronic rhinosinusitis associated with bronchial asthma. Allergol Int 2008;57:429-36.
82. Picado C, Fernandez-Morata JC, Juan M, Roca-Ferrer J, Fuentes M, Xaubet A, Mullol J. Cyclooxygenase-2 mRNA is downexpressed in nasal polyps from aspirin-sensitive asthmatics. Am J Respir Crit Care Med 1999;160:291-6.
83. Cheong HS, Park SM, Kim MO, Park JS, Lee JY, Byun JY, Park BL, Shin HD, Park CS. Genome-wide methylation profile of nasal polyps: relation to aspirin hypersensitivity in asthmatics. Allergy 2011;66:637-44.
84. Liu T, Laidlaw TM, Katz HR, Boyce JA. Prostaglandin E2 deficiency causes a phenotype of aspirin sensitivity that depends on platelets and cysteinyl leukotrienes. Proc Natl Acad Sci U S A 2013;110:16987-92.