

REVIEW

Cysteinyl leukotrienes: multi-functional mediators in allergic rhinitis

M. Peters-Golden*, M. M. Gleason[†] and A. Togias[‡]*University of Michigan, Ann Arbor, MI, USA [†]Merck & Co., Inc., West Point, PA, USA and [‡]Johns Hopkins University, Baltimore, MD, USA**OnlineOpen:** This article is available free online at www.blackwell-synergy.comClinical and
Experimental
Allergy

Correspondence:

Alkis Togias, Divisions of Allergy and
Clinical Immunology and Pulmonary
and Critical Care Medicine, 5501
Hopkins Bayview Circle, Baltimore, MD
21224-6801, USA.
E-mail: atogias@jhmi.edu

Summary

Cysteinyl leukotrienes (CysLTs) are a family of inflammatory lipid mediators synthesized from arachidonic acid by a variety of cells, including mast cells, eosinophils, basophils, and macrophages. This article reviews the data for the role of CysLTs as multi-functional mediators in allergic rhinitis (AR). We review the evidence that: (1) CysLTs are released from inflammatory cells that participate in AR, (2) receptors for CysLTs are located in nasal tissue, (3) CysLTs are increased in patients with AR and are released following allergen exposure, (4) administration of CysLTs reproduces the symptoms of AR, (5) CysLTs play roles in the maturation, as well as tissue recruitment, of inflammatory cells, and (6) a complex inter-regulation between CysLTs and a variety of other inflammatory mediators exists.

Keywords allergic rhinitis, cysteinyl leukotrienes, CysLT₁ receptor, eosinophils, inflammation, leukotriene C₄ synthase, 5-lipoxygenase

Submitted 3 May 2005; revised 23 December 2005; accepted 27 January 2006

Introduction

Allergic rhinitis (AR), which affects approximately 20% of the population in industrialized countries, is associated with substantial morbidity, primarily in the context of reduced quality of life and productivity. Patients with AR experience increased incidence of acute sinusitis and otitis media, both of which can be regarded as causatively linked to nasal disease. In addition, AR is closely related to asthma: more than 80% of patients with atopy and asthma have some form of nasal disease, and the prevalence of asthma in patients with AR can reach 40%, at least fivefold greater than that observed in the general population [1, 2]. Rhinitis also is a major risk factor for the development of asthma. Finally, AR is a prototype of immediate hypersensitivity, and understanding its pathophysiology is of significance for the entire spectrum of allergic conditions.

Identified in the late 1970s [3], leukotrienes are a family of inflammatory lipid mediators synthesized from arachidonic acid by a variety of cells, including mast cells, eosinophils, neutrophils, basophils, and macrophages. The cleavage of arachidonic acid from the nuclear membrane by phospholipase A₂ (PLA₂) initiates the synthesis of the leukotrienes [4]. The subsequent interaction of arachi-

donic acid with the biosynthetic proteins 5-lipoxygenase (5-LO) and 5-lipoxygenase activating protein (FLAP) forms the intermediate 5-HPETE (5-hydroperoxy-6,8,11,14-eicosatetraenoic acid), which is quickly converted to LTA₄. LTA₄ can be converted to LTB₄ by LTA₄ hydrolase or to LTC₄ by LTC₄ synthase. LTC₄ is converted extracellularly to LTD₄ and LTE₄ by sequential amino acid removal from the glutathione tripeptide moiety. LTC₄ is converted to LTD₄ through removal of glutamic acid by γ -glutamyl transpeptidase. Glycine is then removed from LTD₄ by dipeptidase. Consequently, LTC₄, LTD₄, and LTE₄ are together referred to as cysteinyl leukotrienes (CysLTs). LTE₄ is the most stable of the CysLTs and can be measured after excretion into the urine; urinary LTE₄ is often used as a marker of 'whole body' leukotriene synthesis. LTB₄ contains no cysteine, and is, therefore, not a CysLT.

CysLTs exert their actions through activation of two G-protein-coupled receptors: CysLT subtype 1 receptor (CysLT₁) and CysLT₂. CysLT₁ is the most studied and is the target for the drugs montelukast, zafirlukast, and pranlukast. As such, its role in AR and other conditions is better understood. By contrast, there is a paucity of information about the role of CysLT₂, in part because no specific antagonists for this receptor are yet available. Both receptors are present in inflammatory cells, blood vessels, and nasal glandular cells [5–10]. CysLT₁ binds LTD₄ with much greater affinity than either LTC₄ or LTE₄ [11]; in contrast, CysLT₂ binds LTC₄ = LTD₄ > LTE₄. Signaling

Re-use of this article is permitted in accordance with the Creative Commons Deed, Attribution 2.5, which does not permit commercial exploitation.

through both subtypes of the CysLT receptor is mediated, in part, through intracellular calcium mobilization.

CysLTs were originally established as mediators of asthma. However, AR involves immunologically similar reactions, and it was only logical to assume that the CysLTs would be important mediators in this condition. CysLTs and leukotriene receptor occupancy have been linked to several processes in AR, including: (1) dilation of nasal blood vessels and vascular permeability with oedema formation, both leading to nasal congestion, (2) increased mucus production and secretion, leading to rhinorrhea, and (3) recruitment of inflammatory cells from the bloodstream into tissue, thus perpetuating the inflammatory response. However, there is a growing body of evidence suggesting that CysLTs are multi-functional mediators playing a broader role in the inflammation that characterizes allergic disorders such as AR.

This article reviews the data for the role of CysLTs as multi-functional mediators in AR. We will review the evidence that: (1) CysLTs are released from inflammatory cells that participate in AR, (2) receptors for CysLTs are located in nasal tissue, (3) CysLTs are increased in patients with AR and are released following allergen exposure, (4) CysLTs produce symptoms of AR, (5) CysLTs play a role in bone marrow production and tissue recruitment of inflammatory cells, and (6) there is a complex inter-regulation between CysLTs and a variety of other inflammatory mediators.

Cells that are linked to the pathogenesis of allergic rhinitis produce and release cysteinyl leukotrienes

Mast cells, basophils, eosinophils, dendritic cells, monocytes/macrophages, and T lymphocytes collectively initiate

and perpetuate mucosal inflammation in AR. The IgE-bearing mast cells and basophils have the greatest capacity to produce CysLTs, but eosinophils, dendritic cells, monocytes/macrophages, and T lymphocytes also have been shown to release CysLTs (Table 1). Basophils produce more than 100-fold higher amounts of CysLTs compared with eosinophils [12, 13]. Eosinophils isolated from patients with AR released significantly higher levels of CysLTs than eosinophils isolated from healthy subjects following stimulation with the calcium ionophore A23187 [14]. Recently, expression of the CysLT biosynthetic proteins 5-LO, FLAP, and LTC₄ synthase was demonstrated in inflammatory cells present in the nasal secretions of symptomatic patients with seasonal AR [15]. Most of the cells expressing these proteins were eosinophils and mononuclear cells; interestingly, only 30% of mast cells and basophils expressed these enzymes. Many of the same inflammatory cells that secrete CysLTs also express the cell surface CysLT₁ receptor (Table 1), suggesting an autoregulatory mechanism.

Receptors for cysteinyl leukotrienes are found in tissue and on cells that are involved in allergic rhinitis inflammation and symptoms

Using *in situ* hybridization and immunohistochemical techniques, the CysLT₁ receptor has been localized to nasal mucosal interstitial cells, glandular epithelium, and a variety of inflammatory cells (Table 1). Mast cells, neutrophils, eosinophils, monocytes, and macrophages isolated from nasal lavage fluid of patients with active AR express the CysLT₁ receptor [15]. CysLT₁ receptor mRNA and protein have been found on blood vessels, interstitial cells, eosinophils, mast cells, monocytes/

Table 1. Studies demonstrating cells that express the CysLT₁ receptor and cells that synthesize cysteinyl leukotrienes (CysLTs)

Cell type	Express CysLT ₁ receptor	CysLT synthesis	
		Production of CysLTs	Presence of CysLT synthetic enzymes
Basophils	[15, 17]	[176–178]	5-LO, FLAP, LTC ₄ Syn [15]
Mast Cells	[15, 16, 18, 20, 179]	[57, 129, 176, 180–182]	5-LO, FLAP, LTC ₄ Syn [15, 57]
Monocytes	[5, 15–17]	[183, 184]	5-LO, FLAP, LTC ₄ Syn [15]
Eosinophils	[5, 15–17, 20, 119, 156, 185]	[14, 163, 186–190]	5-LO, FLAP, LTC ₄ Syn [15]
Dendritic cells	[39, 40]	[39]	5-LO and FLAP [42, 191]; FLAP, 5-LO and LTC ₄ Syn [39]
Macrophages	[11, 15–17, 20, 21, 192]		5-LO, FLAP, LTC ₄ Syn [15]
T lymphocytes	[5, 20, 193]	[194]	
B lymphocytes	[17]		
Neutrophils	[5, 15, 16, 20]	[195]	5-LO, FLAP [15]
Haematopoietic stem cells	[17, 19]	[91, 93]	5-LO [19]
Epithelial cells	–	[196]	LTC ₄ Syn [15]
Glandular epithelium	[16, 69]		
Endothelial cells	[16, 197]	[91, 197]	
Smooth muscle cells	[11, 17]	–	

CysLT₁ receptor, cysteinyl leukotriene subtype 1 receptor; 5-LO, 5-lipoxygenase enzyme; FLAP, 5-lipoxygenase activating protein; LTC₄Syn, LTC₄synthase.

macrophages, neutrophils, and glandular and vascular endothelium of human nasal mucosal tissue of patients undergoing turbinectomy [16]. Using a panel of peripheral blood cell markers, the presence of the CysLT₁ receptor also has been demonstrated on circulating eosinophils, B lymphocytes, basophils, monocytes, macrophages, and on CD34⁺ haematopoietic stem cells [5, 15, 17–20].

CysLT₁ expression is subject to regulation *in vitro* and *in vivo*. For example, cytokines have been shown to enhance CysLT₁ expression in leucocytes and mesenchymal cells *in vitro* [21]. Sousa et al. [20] studied the expression and regulation of the CysLT₁ receptor on nasal mucosal inflammatory cells from aspirin-sensitive and non-aspirin-sensitive patients with rhinosinusitis and polyps treated with lysine aspirin or placebo. Compared with the non-aspirin-sensitive patients, the absolute number of cells and the percentage of CD45⁺ leucocytes expressing the CysLT₁ receptor, but not the LTB₄ receptor, was higher in the aspirin-sensitive patients. Desensitization with lysine aspirin selectively reduced the number of CD45⁺ leucocytes expressing the CysLT₁ receptor, but not the LTB₄ receptor, suggesting a specific receptor-regulating mechanism associated with the therapeutic benefit of aspirin desensitization in patients with asthma and AR [22]. These data by Sousa and coworkers are the first to demonstrate that CysLT₁ expression can be modulated in disease states and suggest that down-regulation of CysLT₁ receptor could represent a mechanism for therapeutic benefit (in this case, by aspirin desensitization).

CysLT₂ receptors are broadly distributed not only in leucocytes, but also in heart tissue, brain, adrenal glands, and vasculature. Recent studies in mice with deletion [23] or overexpression [24] of CysLT₂ suggest a prominent role for this receptor in mediating vascular permeability, a process to which CysLT₁ also clearly contributes [25]. Emerging data suggest that CysLT₂ may also contribute to fibroproliferation [23, 26] and to inflammatory responses [6] in a manner distinct from CysLT₁.

Cysteinyl leukotrienes are found in patients with allergic rhinitis

Several studies have demonstrated that CysLT levels in nasal fluids are increased in patients with AR (Table 2). CysLTs are significantly elevated in nasal lavage fluid from symptomatic allergic rhinitic patients compared with that from healthy controls [27–29], as well as in nasal lavage fluids during the early and late allergic responses [30–33]. CysLTs were elevated in nasal secretions within 5 min [33] and persisted for 30 min [31] following allergen exposure, and these levels correlated with the duration of symptoms [31]. Ragweed challenge elevated CysLT concentrations in a dose-dependent manner in patients with AR [30, 31], whereas challenge with

Table 2. Cysteinyl leukotrienes (CysLTs) are elevated in patients with allergic rhinitis and conjunctivitis

CysLTs are elevated in	Studies
Nose during natural/seasonal allergen exposure	[27–29, 36, 37, 46, 116, 198]
Urine during natural/seasonal allergen exposure	[72]
Nose after allergen challenge	[30–35, 199–201]
Eyes after allergen challenge	[202, 203]

methacholine [34] or non-relevant allergen [35] had no effect. CysLT levels fluctuated with seasonal allergen exposure [33, 36] and correlated with symptom scores in individuals with AR, but not in non-allergic controls [37]. Levels of CysLTs were also found to increase in nasal fluids when reactions to cold, dry air take place, presumably as a result of mast cell degranulation [38]. This raises the possibility that CysLTs may participate in some forms of rhinitis in the absence of allergic reactions.

Cysteinyl leukotrienes may be participating in the process of allergic sensitization

An allergic response requires processing of the allergen by an antigen-presenting cell. Dendritic cells are potent antigen-presenting cells, initiating the immune response by taking up and presenting antigen to and influencing the polarization of T cells. The effect of CysLTs on dendritic cell function has recently been explored. Dendritic cells express the CysLT₁ receptor [39–41] and the enzymatic machinery necessary to produce CysLTs [39, 41, 42]. CysLTs have been shown to modulate allergen-stimulated dendritic cell production of interleukin (IL) 10, IL-12, IL-5, and interferon γ (IFN- γ) [39] and to enhance dendritic cell-stimulated antigen presentation, T cell proliferation, and T cell cytokine production [41, 43, 44]. They also directly promote dendritic cell migration [40, 45]. CysLTs may influence dendritic cell migration indirectly by increasing the production of dendritic cell chemoattractants, including RANTES [46, 47], macrophage-inflammatory-protein (MIP)-1 α [40, 48], and MIP-3 α [40] from monocytes and macrophages. However, in a recent study, CysLT₁ receptor antagonists did not affect cytokine production by monocyte-derived dendritic cells or monocyte-derived dendritic cell effects on CD4⁺ lymphocytes [41].

Cysteinyl leukotrienes can produce symptoms of allergic rhinitis

Experimental exposure of the nasal mucosa to allergens in sensitized individuals with AR initiates a dual-phase immune response [49]. The early or immediate phase response occurs within minutes of allergen exposure and

is characterized primarily by sneezing, nasal pruritus, rhinorrhea, and acute congestion. The late-phase response occurs hours after allergen exposure and is mainly associated with congestion and, to a lesser extent, rhinorrhea and sneezing.

Upon allergen exposure, crosslinking of IgE receptor activates mast cells and initiates the early allergic response through immediate release of preformed mediators, including histamine, proteases (e.g., tryptase), and tumour necrosis factor α (TNF- α), and the release of newly synthesized mediators, including CysLTs and prostaglandin D₂. CysLTs are released from mast cells within minutes of allergen exposure (Table 3).

Although sneezing occurs within 1–2 min of allergen exposure and decreases rapidly thereafter, some sneezing can occur during the late-phase response. After allergen challenge, the timing of LTC₄ release has been shown to correlate with sneezing [30, 33]. CysLTs do not directly induce sneezing and pruritus [50, 51]; however, CysLTs may have an indirect effect on sneezing, as indicated by the reduction of sneezing with zafirlukast [52] and montelukast [46, 53–57], both leukotriene receptor antagonists, in clinical trials of patients with AR.

Nasal pruritus occurs exclusively during the early-phase response as nerve fibres, probably stimulated by histamine, elicit this sensation. The role of leukotrienes in nasal pruritus is not defined. However, the ability of leukotriene receptor antagonists to relieve the itch of atopic dermatitis [58] and chronic idiopathic urticaria [59, 60] suggests that leukotrienes may contribute to nasal pruritus. This hypothesis is further supported by the ability of montelukast to reduce nasal pruritus in clinical trials of patients with seasonal AR [53, 54, 61, 62].

CysLTs do not directly stimulate sensory nerves. However, in the presence of CysLTs, an electrical stimulus releases increased amounts of neuropeptides from tachykinergic nerves [63, 64]. This suggests that CysLTs may

potentiate neural phenomena such as neurogenic inflammation, which appear to be increased in individuals with AR [65, 66]. In addition, the *in vivo* responsiveness of nasal sensory nerves to histamine may become increased in the presence of CysLTs, as suggested by the work of Konno et al. [67].

Rhinorrhea, resulting from increased glandular activity, is predominantly an early-phase symptom, but it can also occur during the late phase. Application of LTD₄ to the nasal mucosa of patients with AR increased the amount of nasal secretions in a dose-dependent manner, an effect that peaked within 5 min of mediator application [31, 50]. The reduction in rhinorrhea with pranlukast [67], zafirlukast [52], and montelukast [46, 53–56, 61, 68] in clinical trials of patients with AR further supports a role for CysLTs in stimulating nasal secretions. This effect is probably direct, given the fact that the CysLT₁ receptor has been found on human nasal mucosal glands [16, 69].

Nasal congestion is prominent during both the early- and the late-phase response to allergen. The late-phase response occurs in approximately 50% of allergic patients [70]. CysLTs have been shown to cause prolonged congestion (Table 3). CysLTs also increase vascular permeability [71], and the resulting oedema may contribute to the narrowing of nasal passages. Five minutes after topical application of LTD₄, nasal mucosal blood flow and nasal airway resistance increased in a dose-dependent manner [31, 51]. In the study by Okuda et al. [50], the increase in nasal airway resistance did not abate for several hours. Histamine also increases nasal airway resistance, albeit to a maximum at 20 min after application [31]. Urinary LTE₄ levels were found to be significantly higher in patients with AR with severe nasal congestion [72] and less evident in patients with mild congestion [73]. The improvement in nasal congestion following treatment with leukotriene modifiers, measured either by symptom scores [46, 52–56, 74] or airway resistance [61, 67, 68] in clinical

Table 3. Allergen-induced rhinitis and clinical rhinitis outcomes affected by cysteinyl leukotrienes (CysLTs)

Symptom	Studies showing effect
Sneezing	Significantly correlated with CysLTs levels in patients with allergic rhinitis following allergen challenge [30] Significantly improved with LTRA in clinical studies of patients with allergic rhinitis [46, 52–56, 61]
Rhinorrhea	Significantly worsened with intranasal CysLT application [31, 50] Significantly improved with LTRA in studies of patients with allergic rhinitis following allergen challenge [67] Significantly improved with LTRA in clinical studies of patients with allergic rhinitis [46, 52–56, 61, 68]
Nasal pruritus	Significantly improved with LTRA in clinical studies of patients with allergic rhinitis [53, 54, 61, 62]
Congestion	Significantly worsened with intranasal CysLT application [31, 50, 51, 204, 205] Significantly improved with LTRA in clinical studies of patients with allergic rhinitis [46, 52–56, 61, 67, 68, 74]
Itchy throat and palate	Significantly improved with LTRA in clinical studies of patients with allergic rhinitis [52]
Eye symptoms	Significantly improved with LTRA in clinical studies of patients with allergic rhinitis [53–56, 61, 143, 206]
Rhinoconjunctivitis quality of life	Significantly improved with LTRA in clinical studies of patients with allergic rhinitis [53–56, 61, 206]

LTRA, leukotriene receptor antagonist.

trials of patients with AR further implicates CysLTs in mediating nasal congestion. It should be noted that, because of the presence of both CysLT₁ and CysLT₂ receptors in nasal vasculature, and because stimulation of the CysLT₂ receptor appears to increase vascular permeability [24], antagonism of both receptors may offer stronger effects against nasal congestion in AR.

In support of the contribution of CysLTs in mediating individual symptoms of the early- and late-phase allergic response, several CysLT₁ receptor antagonists have been shown to reduce the aggregate of symptoms in clinical trials of patients with AR (Table 3). Pranlukast improved daytime symptoms [75], and zafirlukast improved nasal congestion, sneezing, rhinorrhea, and itchy nose, throat, and palate, although no clear dose-response could be generated [52]. Montelukast has been shown to improve daytime symptoms (congestion, rhinorrhea, sneezing, and nasal pruritus), night-time symptoms (difficulty to sleep, awakenings, and congestion upon awakening), daytime eye symptoms (tearing, itchy, red, and puffy eyes), and quality of life [53–56].

Cysteinyl leukotrienes and cellular inflammation in allergic rhinitis

In the course of natural exposure to aeroallergens, as well as with experimental allergen challenge, various inflammatory cells, including eosinophils, basophils, monocytes, and TH₂ lymphocytes, are elevated in nasal tissue and nasal secretions [76, 77] and correlate with symptoms in patients with AR [78, 81]. Inflammatory cells release various forms of mediators into the nasal mucosa, ranging from symptom-producing substances to pure cytokines that perpetuate chronic inflammation and symptoms. The steps leading to inflammatory cell recruitment are not completely understood, and it is quite likely that the mechanisms of recruitment and activation are unique for each cell type. There is enough evidence in both asthma and AR to support the hypothesis that inflammatory elements generated during local allergic reactions may produce systemic signals affecting circulating cells, cells residing in peripheral lymphoid tissue, and immature cells residing in the bone marrow [2, 9, 82–84]. When contemplating the continuously emerging knowledge on the immunomodulatory properties of the CysLTs, it is reasonable to put forward a hypothesis that these mediators contribute to the systemic inflammation associated with AR. This hypothesis is schematically depicted in Fig. 1.

Step 1: haematopoiesis

The role of eosinophil and basophil progenitors in allergic inflammation and their fluctuation with seasonal exposure has been reviewed [85–87]. CysLTs have been shown

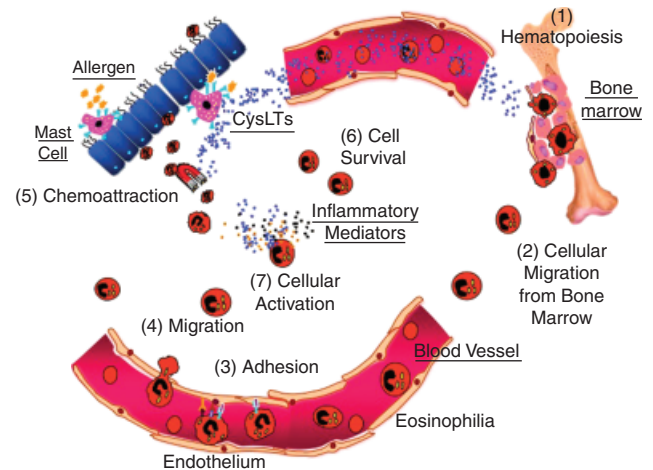


Fig. 1. Cysteinyl leukotrienes (CysLTs) and the Inflammatory Events of Allergic Rhinitis. Crosslinking of immunoglobulin E with allergen initiates release of a variety of mediators from mast cells, including CysLTs. CysLTs play a role in hematopoiesis, cellular migration from bone marrow to the circulation, adhesion of inflammatory cells to the vascular endothelium, migration of cells to the nasal tissue, cell survival, and cellular activity enhancement.

to play a role in leucopoiesis induced by granulocyte-macrophage colony stimulating factor (GM-CSF) [88–90], IL-5 [89], and IL-3. [91] In a mouse model of AR, montelukast was shown to inhibit either bone marrow IL-5- or GM-CSF-responsive eosinophil/basophil colony-forming units and IL-5-stimulated eosinophil maturation [92]. The inhibition of IL-5-dependent proliferation of bone marrow eosinophil–basophil progenitors and GM-CSF-dependent proliferation of peripheral blood eosinophil–basophil progenitors by the leukotriene receptor antagonist montelukast [89] points to the activity of CysLTs through the CysLT₁ receptor on CD34⁺ haematopoietic bone marrow stem cells [17, 19, 93]. Interestingly, these cells express 5-LO [19, 94, 95], and bone marrow cells can produce CysLTs upon *in vitro* stimulation with the calcium ionophore A23187 [91, 93]. These data suggest that CysLTs may be both paracrine and autocrine contributors to haematopoiesis.

Step 2: migration from bone marrow

Chemotaxis and transendothelial migration of CD34⁺ progenitor cells in response to LTD₄ and inhibition by the leukotriene receptor antagonist MK-571 [19] suggest a role for CysLTs in leucocyte migration from the bone marrow into the circulatory system. Chemotaxis and transendothelial migration are preceded by endothelial adhesion. LTD₄ up-regulated adhesion of human peripheral blood CD34⁺ progenitors to bone marrow endothelium; this was blocked by MK-571 and antibodies against β_1 and β_2 integrins [96].

Step 3: adhesion to post-capillary venules

Leucocyte adhesion to the vascular wall is the first step in recruitment and migration into nasal tissue. Adhesion molecules are expressed by the nasal endothelium of patients with AR within 24 h after nasal allergen challenge [97]. CysLTs enhance leucocyte adhesion by increasing the expression of the adhesion molecules P-selectin and soluble sialyl Lewis^x [98, 99], α M β ₂ [100], β ₂ integrins [101], and Mac-1 [102]. CysLT-induced leucocyte adhesion and adhesion molecule expression is inhibited by the leukotriene receptor antagonists montelukast [102] and pranlukast [101]. Nagata *et al.* [103] observed that eosinophil adhesion via β ₂ integrins to intercellular cell adhesion molecule 1 (ICAM-1) augmented eosinophil LTC₄ generation. These data suggest a positive feedback mechanism that increases the production of CysLTs at the site of eosinophil adhesion.

Steps 4 and 5: migration and chemoattraction

Transendothelial migration of leucocytes across the vessel wall into the tissue follows cellular adhesion. CysLTs are direct chemoattractants for eosinophils and have been shown to enhance eosinophil migration *in vivo* [104–106] and *in vitro* [92, 102, 106, 107]. This phenomenon is dose-dependently inhibited by leukotriene receptor antagonism with FPL 55712 [106], SK&F 104353 [107] and montelukast [102, 108]. Eotaxin is a selective chemoattractant for eosinophils. The role of CysLTs in eosinophil recruitment is further implicated by the observation that LTC₄ increases eotaxin release from endothelial cells [109, 110] and from IL-13-primed fibroblasts [111], which is blocked by montelukast and pranlukast. Finally, montelukast treatment has been shown to reduce eosinophils in nasal mucosa of adults [46] and children [61] with AR.

Step 6: cell survival

Tissue eosinophilia is a function of both the influx of eosinophils into the nasal mucosa as well as their half-life (survival). CysLTs increase eosinophil survival time [112], and this effect is inhibited by leukotriene receptor antagonists [112, 113].

Step 7: cellular activation

Once in the nasal tissue, CysLTs also promote inflammation by enhancing the activity of inflammatory cells. This section focuses on eosinophil activation, but the ability of CysLTs to affect the function of other inflammatory cells, including monocytes, basophils, mast cells, and T lymphocytes, is also described.

Activated eosinophils release a variety of inflammatory mediators and probably play a significant role in allergic

disease. For example, eosinophilic cationic protein (ECP) is toxic to epithelial tissue; a consequence of such toxicity may be exposure of sensory nerve fibres to environmental irritants. Major basic protein (MBP), on the other hand, can inhibit the ability of acetylcholine to prevent further acetylcholine release from peripheral parasympathetic nerves by deactivating the M2 receptor [114]. Elevated ECP in the nasal fluid of patients with AR [115] correlates with an increase in LTC₄ [116], and treatment with montelukast decreases ECP levels in the serum of adults [117] and in nasal washes from pediatric patients [118]. A significant correlation between CysLTs and eosinophilic protein X, a marker of eosinophilic activity, has also been demonstrated [27]. Superoxide radicals mediate inflammation through oxidative damage in cells, and LTD₄ was shown to increase superoxide radical levels in eosinophils *in vitro* [100]. Eosinophil-derived neurotoxin (EDN) is another cytotoxic mediator. IL-5-induced release of EDN was enhanced by LTD₄ [119] and, in another study, LTD₄-induced EDN release by peripheral blood eosinophils of healthy subjects [120]. The effects of LTD₄ on superoxide radicals and EDN were blocked by pranlukast [120].

In clinical studies, the leukotriene receptor antagonist montelukast reduced peripheral blood eosinophil numbers in adults [53–56] and children [61, 121] with AR. Taken together, the effects of CysLTs on eosinophil differentiation, maturation, proliferation, adhesion molecule expression, migration, survival, and activation described above are consistent with a role of these mediators in local and systemic allergic inflammation.

Bidirectional modulation between cysteinyl leukotrienes and other inflammatory mediators

A complex network of interactions exists between CysLTs and a variety of inflammatory mediators (Fig. 2).

Cysteinyl leukotrienes enhance the production and activity of inflammatory mediators

In patients with established allergic inflammation, immune responses to allergens are TH₂ polarized, resulting in a preponderance of TH₂ relative to the TH₁ cytokines [122, 123]. *In vitro* and *in vivo* evidence suggests that TH₂ cytokines can be modulated by CysLTs. *In vitro*, CysLTs or CysLT₁ receptor antagonism have been shown to modulate the production of IL-3 [124], IL-4 [124, 125], IL-5, [124, 126], IL-10 [127], and GM-CSF [113, 124]. In patients with perennial AR, 4 weeks of treatment with pranlukast suppressed nasal mucosal production of IL-4 and IL-5 [46]. A 2-week treatment with montelukast decreased IL-4 and IL-13 levels in nasal lavage secretions from children with AR [120]. Also, serum IL-5 levels were reduced in children with asthma after 6 weeks of treatment with montelukast [129].

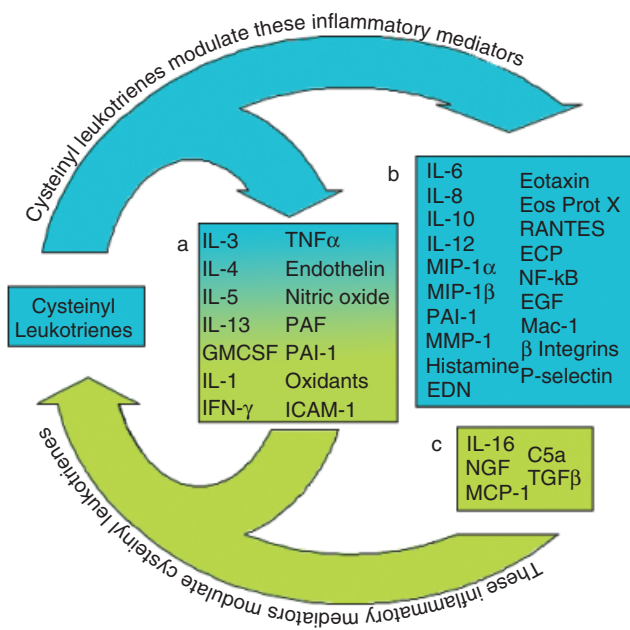


Fig. 2. Interactions between cysteinyl leukotrienes (CysLTs) and inflammatory mediators. (a) Studies have demonstrated bidirectional regulation of these mediators; i.e., activity of these mediators can be modulated by CysLTs and, in turn, these mediators can modulate CysLTs activity. (b) Studies have demonstrated that the activity of these mediators can be modulated by CysLTs. (c) Studies have demonstrated that these mediators can modulate activity of CysLTs.

CysLTs may also affect a variety of non-TH₂ mediators that play a role in inflammation associated with AR. The levels of the pro-inflammatory cytokine IL-6 were decreased from peripheral blood mononuclear cells [130] and those of the TH₁ cytokine IFN- γ were increased from mononuclear cells [131] from healthy volunteers by CysLT₁ antagonism with pranlukast and montelukast, respectively. In patients with AR, treatment with pranlukast suppressed production of IL-1 β and IL-8 in the nasal mucosa [46], and treatment with montelukast increased IFN- γ levels in nasal secretions [128]. The increased production of IFN- γ in 5-LO knockout mice supports the regulation of this cytokine by products of the 5-LO pathway [132]. The level and activity of a variety of other mediators have been shown to be modulated by CysLTs. For example, several *in vitro* studies have demonstrated that levels of TNF- α produced by mast cells [126] and macrophages [48] are enhanced by CysLTs and decreased by CysLT₁ receptor antagonism [48, 126, 133]. In patients with perennial AR, 4 weeks of treatment with pranlukast suppressed nasal mucosal production of TNF- α [46]. NF- κ B is a transcription factor involved in regulating expression of proinflammatory cytokines such as IL-1, IL-6, IL-8, and TNF- α . Pranlukast and MK-571 have been shown to inhibit NF- κ B activation in monocytes [130, 133]. In human mast cells, LTC₄ and LTD₄ increased

the release of macrophage inflammatory protein-1 β (MIP-1 β), and this was blocked by MK-571 [126]. RANTES, which is produced by T cells, is a potent chemoattractant for monocytes, lymphocytes, and eosinophils. The level of RANTES in nasal mucosa of patients with perennial AR was decreased after 4 weeks treatment with pranlukast [46].

CysLTs have also been shown to affect mediators of inflammatory tissue growth and repair. For example, the proliferative effects of epidermal growth factor (EGF) on smooth muscle cells in culture were potentiated by LTD₄ [134]. The proliferative effects of insulin-like growth factor (IGF) on smooth muscle cells in culture were also potentiated by LTD₄ induction of matrix metalloproteinases (MMP-1) [135]. Insulin-like growth factor binding proteins (IGFBP) limit the ability of IGF to enhance differentiation, growth, and proliferation of cells. Proteolysis of IGFBP by MMP-1 removes inhibition of the IGF effects. Plasminogen activator inhibitor type-1 (PAI-1) promotion of abnormal tissue repair plays a role in airway remodeling; LTD₄ increased, and montelukast decreased, production of PAI-1 by mast cells [136].

There is evidence for an interaction between CysLTs and histamine, another pivotal mediator of allergic reactions. LTD₄ enhanced histamine-induced elevation of cytosolic calcium levels in cultured embryonic carcinoma cells [137] and prostaglandin E₂ (PGE₂) production from human monocytes and smooth muscle cells, as well as mouse macrophages [138]. The LTD₄-enhanced histamine-induced PGE₂ production was coincident with the appearance of additional histamine receptors [138]. These *in vitro* observations are in concordance with the *in vivo* effects of CysLT₁ antagonism on nasal responsiveness to histamine described earlier [67]. The modulation of endothelin by CysLTs has also been demonstrated [139].

Exhaled nitric oxide (NO) is a marker of airway inflammation. Montelukast has been shown to reduce levels of exhaled NO in clinical trials with asthmatic adults [140, 141] and children [142, 143], but no studies have evaluated whether nasal NO is also affected. *In vitro*, LTC₄ increased NO release from polymorphonuclear leucocytes [144] and from macrophages [145]. Ethacrynic acid, an inhibitor of LTC₄ production, has been shown to inhibit NO production by mouse peritoneal macrophages [146]. Ovalbumin (OVA) challenge in OVA-sensitized rats increased lung-inducible nitric oxide synthase (iNOS) expression, which was decreased by treatment with montelukast [147]. Taken together, these data suggest a mechanism for the reduction in eNO observed clinically with montelukast. Superoxide radical levels in eosinophils have also been shown to be increased by LTD₄ [100] and blocked by pranlukast [120].

Inflammatory mediators enhance the production and activity of cysteinyl leukotrienes

In addition to the effects of CysLTs on other inflammatory mediators, the converse is also true, in that various inflammatory mediators can exert regulatory effects on CysLTs. Several studies have demonstrated the ability of TH₂ cytokines to enhance the synthesis of CysLTs as well as the expression of the CysLT₁ receptor. IL-5 increases the expression of FLAP and the translocation of 5-LO to the nucleus of eosinophils, which is accompanied by an increase in CysLT synthesis [148]. IL-3, IL-4, and IL-5 augment CysLT production by mast cells through induction of LTC₄ synthase and 5-LO nuclear translocation [57]. The combination of IL-3 and C5a stimulated the production of LTC₄ in basophils [149]. IL-3 [13, 149, 150], IL-5 [13, 149], and GM-CSF [149, 151, 152] stimulated CysLT synthesis in eosinophils, basophils, and T lymphocytes. GM-CSF also stimulated LTC₄ synthesis through increased PLA₂ mobilization of arachidonic acid in macrophages [153] and increased CysLT synthetic capacity through increased 5-LO [154] and FLAP expression [154, 155] in monocytes and neutrophils. TH₂ cytokines also up-regulate CysLT₁ receptors, a mechanism that, theoretically, can enhance CysLT actions. IL-5 [156], IL-4 [21, 126], and IL-13 [21, 157] up-regulated the expression of functionally active CysLT₁ receptors on HL-60 cells differentiated into eosinophils (IL-5), monocytes (IL-4 and IL-13), macrophages (IL-4 and IL-13), and smooth muscle cells (IL-13). In support of the interaction between IL-13 and CysLTs, leukotriene receptor antagonism with MK-571 inhibited IL-13-induced CysLT synthesis in bronchoalveolar lavage (BAL) fluid in a mouse model of asthma [158]. The full range of interaction between TH₂ cytokines and leukotrienes was illustrated in an *in vitro* study, which demonstrated that IL-13 increased CysLT₁ receptor expression on lung-derived fibroblasts, subsequently enabling the cells to respond to LTC₄ stimulation by releasing functionally active eotaxin, which subsequently promoted eosinophil chemotaxis and migration [111]. However, CysLT₁ receptors have not been observed on nasal polyp-derived fibroblasts [159].

Non-TH₂ inflammatory mediators also regulate CysLT synthesis and receptor activity. CysLT₁ receptor expression on smooth muscle cells and endothelial cells has been demonstrated to increase when stimulated with IFN- γ [157, 160] and IL-1 β [161]. IL-16 is increased in nasal mucosa of patients with AR during seasonal allergy exposure [162] and is a chemoattractant for eosinophils. In human eosinophils, IL-16-stimulated eotaxin release was followed by activation of CCR3 receptors and enhanced LTC₄ and IL-4 release. These data suggest that IL-16-stimulated LTC₄ and IL-4 release may occur through autocrine eotaxin activation of CCR3 receptors [163]. Transforming growth factor β 1 (TGF- β ₁) and, to a lesser

extent, TGF- β ₂ up-regulated 5-LO activity in HL-60 cells induced to granulocytic differentiation by dimethyl sulfoxide [164], LTC₄ synthase expression in THP-1 macrophages [165], and CysLT₁ receptor expression in smooth muscle cells [157]. The ability of TGF- β ₁ and LTD₄ to synergistically enhance smooth muscle proliferation [157] functionally illustrates the inter-regulation of these two mediators. TNF- α [166], MCP-1 [149], C5a [149], platelet-activating factor (PAF) [167, 168], and endothelin [169] have been shown to enhance CysLT production by eosinophils, basophils, and mast cells, whereas nerve growth factor (NGF) [166] and oxidants [170] have been shown to reduce CysLT production. Finally, NO has been shown to increase CysLT production from human mast cells [171].

Summary/conclusion

A substantial body of research reviewed in this article indicates that CysLTs satisfy Koch's postulates as mediators of AR, as (i) they are overproduced in the nasal mucosa of patients with the disease; (ii) they reproduce many clinical features of AR; and (iii) pharmacologic agents that block their synthesis or receptor-mediated actions attenuate the manifestations of AR. Recent studies have also elucidated a variety of mechanisms, other than direct symptom production, by which CysLTs promote AR. They have revealed that these lipid mediators participate in the genesis of systemic immune responses to antigen and in leucocyte accumulation, survival, and activation in affected tissues. One particularly compelling, but underappreciated, aspect of the involvement of CysLTs in allergic disease is the bidirectional interplay between CysLTs and other inflammatory mediators, such as cytokines, chemokines, growth factors, histamine, and reactive oxygen and nitrogen species. In this regard, leukotrienes can modulate the generation of a variety of mediators, and other mediators can modulate leukotriene actions by influencing both their synthesis and the expression of their receptors. Although a role for CysLTs in the pathogenesis of asthma was recognized first – involving many of these same mechanisms – the subsequent recognition of their role in AR supports the concept of a unified airway response to common triggering events.

It should be clearly stated that CysLTs represent only one of the participants of the allergic response. Other biologic products, including histamine or PGD₂, play important roles. For example, histamine, acting through its H₁ receptors, not only generates acute nasal symptoms, but it also has several properties that are not identifiable on the basis of its acute action on the nasal mucosa, including immunomodulatory activities and interactions with other mediators [172, 173]. CysLT₁ receptor antagonists, like H₁ receptor antagonists, have well-established

clinical effects in AR. In fact, their overall clinical effectiveness appears to be of similar magnitude [174]. These antagonists are less effective compared with nasal glucocorticosteroids because the latter agents have a wider target spectrum. It should be kept in mind, however, that the systemic nature of treatment that CysLT₁ receptor antagonists and antihistamines provide may have additional benefits that are not identifiable by the short-term studies that target the symptoms of AR [175]. This concept requires exploration.

Acknowledgements

The authors thank Carolyn Hustad, PhD, for editing and formatting the manuscript and Denise Stek and Jennifer Pawlowski for help with creating the reference list.

References

- Leynaert B, Bousquet J, Neukirch C, Liard R, Neukirch F. Perennial rhinitis: an independent risk factor for asthma in nonatopic subjects. Results from the European Community Respiratory Health Survey. *J Allergy Clin Immunol* 1999; **104**:301–4.
- Togias A. Rhinitis and asthma: evidence for respiratory system integration. *J Allergy Clin Immunol* 2003; **111**:1171–83.
- Murphy RC, Hammarstrom S, Samuelsson B. Leukotriene C: a slow-reacting substance from murine mastocytoma cells. *Proc Natl Acad Sci USA* 1979; **76**:4275–9.
- Drazen JM, Israel E, O'Byrne PM. Treatment of asthma with drugs modifying the leukotriene pathway. *N Engl J Med* 1999; **340**:197–206.
- Mita H, Hasegawa M, Saito H, Akiyama K. Levels of cysteinyl leukotriene receptor mRNA in human peripheral leucocytes: significantly higher expression of cysteinyl leukotriene receptor 2 mRNA in eosinophils. *Clin Exp Allergy* 2001; **31**:1714–23.
- Mellor EA, Frank N, Soler D *et al.* Expression of the type 2 receptor for cysteinyl leukotrienes (CysLT_{2R}) by human mast cells: functional distinction from CysLT_{1R}. *Proc Natl Acad Sci USA* 2003; **100**:11589–93.
- Gauvreau GM, Boulet LP, Postma DS *et al.* Effect of low-dose ciclesonide on allergen-induced responses in subjects with mild allergic asthma. *J Allergy Clin Immunol* 2005; **116**:285–91.
- Steinke JW, Borish L. Leukotriene receptors in rhinitis and sinusitis. *Curr Allergy Asthma Rep* 2004; **4**:217–23.
- Borish L. Allergic rhinitis: systemic inflammation and implications for management. *J Allergy Clin Immunol* 2003; **112**:1021–31.
- Corrigan C, Mallett K, Ying S *et al.* Expression of the cysteinyl leukotriene receptors cysLT₁(1) and cysLT₂(2) in aspirin-sensitive and aspirin-tolerant chronic rhinosinusitis. *J Allergy Clin Immunol* 2005; **115**:316–22.
- Lynch KR, O'Neill GP, Liu Q *et al.* Characterization of the human cysteinyl leukotriene CysLT₁ receptor. *Nature* 1999; **399**:789–93.
- Eglite S, Pluss K, Dahinden CA. Requirements for C5a receptor-mediated IL-4 and IL-13 production and leukotriene C₄ generation in human basophils. *J Immunol* 2000; **165**:2183–9.
- Takafuji S. IL-3 and IL-5 prime normal human eosinophils to produce leukotriene C₄ in response to soluble agonists. *J Immunol* 1991; **147**:3855–61.
- Kohi F, Miyagawa H, Agrawal DK, Bewtra AK, Townley RG. Generation of leukotriene B₄ and C₄ from granulocytes of normal controls, allergic rhinitis, and asthmatic subjects. *Ann Allergy* 1990; **65**:228–32.
- Figuroa 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.
- Shirasaki H, Kanaizumi E, Watanabe K *et al.* Expression and localization of the cysteinyl leukotriene 1 receptor in human nasal mucosa. *Clin Exp Allergy* 2002; **32**:1007–12.
- Figuroa DJ, Breyer RM, Defoe SK *et al.* Expression of the cysteinyl leukotriene 1 receptor in normal human lung and peripheral blood leukocytes. *Am J Respir Crit Care Med* 2001; **163**:226–33.
- Mellor EA, Maekawa A, Austen KF, Boyce JA. Cysteinyl leukotriene receptor 1 is also a pyrimidineric receptor and is expressed by human mast cells. *Proc Natl Acad Sci USA* 2001; **98**:7964–9.
- Bautz F, Denzlinger C, Kanz L, Mohle R. Chemotaxis and transendothelial migration of CD34(+) hematopoietic progenitor cells induced by the inflammatory mediator leukotriene D₄ are mediated by the 7-transmembrane receptor cyslt1. *Blood* 2001; **97**:3433–40.
- 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**:1524–6.
- Thivierge M, Stankova J, Rola-Pleszczynski M. IL-13 and IL-14 up-regulate cysteinyl leukotriene 1 receptor expression in human monocytes and macrophages. *J Immunol* 2001; **167**:2855–60.
- Stevenson DD, Simon RA, Mathison DA. Aspirin-sensitive asthma: tolerance to aspirin after positive oral aspirin challenges. *J Allergy Clin Immunol* 1980; **66**:82–8.
- Beller TC, Maekawa A, Friend DS, Austen KF, Kanaoka Y. Targeted gene disruption reveals the role of the cysteinyl leukotriene 2 receptor in increased vascular permeability and in bleomycin-induced pulmonary fibrosis in mice. *J Biol Chem* 2004; **279**:46129–34.
- Hui Y, Cheng Y, Smalera I *et al.* Directed vascular expression of human cysteinyl leukotriene 2 receptor modulates endothelial permeability and systemic blood pressure. *Circulation* 2004; **110**:3360–6.
- 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**:20820–9.
- Beller TC, Friend DS, Maekawa A, Lam BK, Austen KF, Kanaoka Y. Cysteinyl leukotriene 1 receptor controls the severity of chronic pulmonary inflammation and fibrosis. *Proc Natl Acad Sci USA* 2004; **101**:3047–52.

- 27 Knani J, Campbell A, Enander I, Peterson CG, Michel FB, Bousquet J. Indirect evidence of nasal inflammation assessed by titration of inflammatory mediators and enumeration of cells in nasal secretions of patients with chronic rhinitis. *J Allergy Clin Immunol* 1992; **90**:880–9.
- 28 Kojima T, Asakura K. A study of chemical mediators in patients with allergic rhinitis. 3. Release of histamine and leukotrienes from *in vitro* nasal mucosa. *Nippon Jibiinkoka Gakkai Kaiho* 1991; **94**:587–93.
- 29 de Graaf-in't Veld, Garrelts IM, Koenders S, Gerth VW. Relationship between nasal hyperreactivity, mediators and eosinophils in patients with perennial allergic rhinitis and controls. *Clin Exp Allergy* 1996; **26**:903–8.
- 30 Creticos PS, Peters SP, Adkinson NF, Jr. *et al*. Peptide leukotriene release after antigen challenge in patients sensitive to ragweed. *N Engl J Med* 1984; **310**:1626–30.
- 31 Miadonna A, Tedeschi A, Leggieri E *et al*. Behavior and clinical relevance of histamine and leukotrienes C4 and B4 in grass pollen-induced rhinitis. *Am Rev Respir Dis* 1987; **136**:357–62.
- 32 Pipkorn U, Proud D, Lichtenstein LM, Kagey-Sobotka A, Norman PS, Naclerio RM. Inhibition of mediator release in allergic rhinitis by pretreatment with topical glucocorticosteroids. *N Engl J Med* 1987; **316**:1506–10.
- 33 Wang D, Clement P, Smits J, De Waele M, Derde MP. Correlations between complaints, inflammatory cells and mediator concentrations in nasal secretions after nasal allergen challenge and during natural allergen exposure. *Int Arch Allergy Immunol* 1995; **106**:278–85.
- 34 Shaw RJ, Fitzharris P, Cromwell O, Wardlaw AJ, Kay AB. Allergen-induced release of sulphidopeptide leukotrienes (SRS-A) and LTB4 in allergic rhinitis. *Allergy* 1985; **40**:1–6.
- 35 Ophir D, Fink A, Eliraz A, Tabachnik E, Bentwich Z. Allergen-induced leukotriene production by nasal mucosa and peripheral blood leukocytes. *Arch Otolaryngol Head Neck Surg* 1988; **114**:522–4.
- 36 Skoner DP, Lee L, Doyle WJ, Boehm S, Fireman P. Nasal physiology and inflammatory mediators during natural pollen exposure. *Ann Allergy* 1990; **65**:206–10.
- 37 Volovitz B, Osur SL, Bernstein JM, Ogra PL. Leukotriene C4 release in upper respiratory mucosa during natural exposure to ragweed in ragweed-sensitive children. *J Allergy Clin Immunol* 1988; **82**:414–8.
- 38 Togias AG, Naclerio RM, Peters SP *et al*. Local generation of sulfidopeptide leukotrienes upon nasal provocation with cold, dry air. *Am Rev Respir Dis* 1986; **133**:1133–7.
- 39 Machida I, Matsuse H, Kondo Y *et al*. Cysteinyl leukotrienes regulate dendritic cell functions in a murine model of asthma. *J Immunol* 2004; **172**:1833–8.
- 40 Parameswaran K, Liang H, Fanat A, Watson R, Snider DP, O'Byrne PM. Role for cysteinyl leukotrienes in allergen-induced change in circulating dendritic cell number in asthma. *J Allergy Clin Immunol* 2004; **114**:73–9.
- 41 Saeki S, Matsuse H, Kondo Y *et al*. Effects of antiasthmatic agents on the functions of peripheral blood monocyte-derived dendritic cells from atopic patients. *J Allergy Clin Immunol* 2004; **114**:538–44.
- 42 Spanbroek R, Hildner M, Steinhilber D *et al*. 5-lipoxygenase expression in dendritic cells generated from CD34(+) hematopoietic progenitors and in lymphoid organs. *Blood* 2000; **96**:3857–65.
- 43 Chibana K, Ishii Y, Asakura T, Fukuda T. Effect of cysteinyl leukotriene on the antigen presenting function of monocyte-derived dendritic cells. *Am J Respir Crit Care Med* 2004; **169**:A62.
- 44 Okunishi K, Dohi M, Nakagome K, Tanaka R, Yamamoto K. A novel role of cysteinyl leukotrienes to promote dendritic cell activation in the antigen-induced immune responses in the lung. *J Immunol* 2004; **173**:6393–402.
- 45 Robbiani DF, Finch RA, Jager D, Muller WA, Sartorelli AC, Randolph GJ. The leukotriene C(4) transporter MRP1 regulates CCL19 (MIP-3beta, ELC)-dependent mobilization of dendritic cells to lymph nodes. *Cell* 2000; **103**:757–68.
- 46 Ueda T, Takeno S, Furukido K, Hirakawa K, Yajin K. Leukotriene receptor antagonist pranlukast suppresses eosinophil infiltration and cytokine production in human nasal mucosa of perennial allergic rhinitis. *Ann Otol Rhinol Laryngol* 2003; **112**:955–61.
- 47 Kawano T, Matsuse H, Kondo Y *et al*. Cysteinyl leukotrienes induce nuclear factor kappa b activation and RANTES production in a murine model of asthma. *J Allergy Clin Immunol* 2003; **112**:411–9.
- 48 Menard G. Priming of alveolar macrophages by leukotriene D4; potentiation of inflammation. *Am J Respir Cell Mol Biol* 2000; **23**:572–7.
- 49 Togias AG. Systemic immunologic and inflammatory aspects of allergic rhinitis. *J Allergy Clin Immunol* 2000; **106**:S247–50.
- 50 Okuda M, Watase T, Mezawa A, Liu CM. The role of leukotriene D4 in allergic rhinitis. *Ann Allergy* 1988; **60**:537–40.
- 51 Bisgaard H, Olsson P, Bende M. Effect of leukotriene D4 on nasal mucosal blood flow, nasal airway resistance and nasal secretion in humans. *Clin Allergy* 1986; **16**:289–97.
- 52 Donnelly AL, Glass M, Minkwitz MC, Casale TB. The leukotriene D4-receptor antagonist, ICI 204,219, relieves symptoms of acute seasonal allergic rhinitis. *Am J Respir Crit Care Med* 1995; **151**:1734–9.
- 53 Philip G, Malmstrom K, Hampel FC *et al*. Montelukast for treating seasonal allergic rhinitis: a randomized, double-blind, placebo-controlled trial performed in the spring. *Clin Exp Allergy* 2002; **32**:1020–8.
- 54 Nayak AS, Philip G, Lu S, Malice MP, Reiss TF. Montelukast Fall Rhinitis Investigator Group. Efficacy and tolerability of montelukast alone or in combination with loratadine in seasonal allergic rhinitis: a multicenter, randomized, double-blind, placebo-controlled trial performed in the fall. *Ann Allergy Asthma Immunol* 2002; **88**:592–600.
- 55 van Adelsberg J, Philip G, Menten J, Malice MP, Reiss TF. Flexible dosing of montelukast for treatment of seasonal allergic rhinitis: morning or evening. *J Allergy Clin Immunol* 2003; **111**:S146.
- 56 van Adelsberg J, Philip G, Pedinoff AJ *et al*. Montelukast improves symptoms of seasonal allergic rhinitis over a 4-week treatment period. *Allergy* 2003; **58**:1268–76.
- 57 Hsieh F. 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 C4 synthase expression by interleukin 4. *J Exp Med* 2001; **193**:123–33.

- 58 Friedmann PS, Perzanowska M, McGuire C *et al.* New therapeutic indications for Cys-LT-1 antagonists: atopic dermatitis and urticaria. *Clin Exp Allergy Rev* 2001; 1:156–9.
- 59 Nettis E, Dambra P, D'Oronzio L, Paola Loria M, Ferrannini A, Tursi A. Comparison of montelukast and fexofenadine for chronic idiopathic urticaria. *Arch Dermatol* 2001; 137:99–100.
- 60 Pacor ML, Di Lorenzo G, Corrocher R. Efficacy of leukotriene receptor antagonist in chronic urticaria. A double-blind, placebo-controlled comparison of treatment with montelukast and cetirizine in patients with chronic urticaria with intolerance to food additive and/or acetylsalicylic acid. *Clin Exp Allergy* 2001; 31:1607–14.
- 61 Hsieh JC, Lue KH, Lai DS, Sun HL, Lin YH. A comparison of cetirizine and montelukast for treating childhood perennial allergic rhinitis. *Pediatr Asthma Allergy Immunol* 2004; 17:59–69.
- 62 Kurowski M, Kuna P, Gorski P. Montelukast plus cetirizine in the prophylactic treatment of seasonal allergic rhinitis: influence on clinical symptoms and nasal allergic inflammation. *Allergy* 2004; 59:280–8.
- 63 Ellis JL, Udem BJ. Role of peptidoleukotrienes in capsaicin-sensitive sensory fibre-mediated responses in guinea-pig airways. *J Physiol* 1991; 436:469–84.
- 64 McAlexander MA, Myers AC, Udem BJ. Inhibition of 5-lipoxygenase diminishes neurally evoked tachykinergic contraction of guinea pig isolated airway. *J Pharmacol Exp Ther* 1998; 285:602–7.
- 65 Sanico AM, Atsuta S, Proud D, Togias A. Plasma extravasation through neuronal stimulation in human nasal mucosa in the setting of allergic rhinitis. *J Appl Physiol* 1998; 84:537–43.
- 66 Sanico AM, Philip G, Proud D, Naclerio RM, Togias A. Comparison of nasal mucosal responsiveness to neuronal stimulation in non-allergic and allergic rhinitis: effects of capsaicin nasal challenge. *Clin Exp Allergy* 1998; 28:92–100.
- 67 Konno A, Yamakoshi T, Usui N. Clinical evaluation of leukotriene antagonist, ONO-1078 (pranlukast hydrate), on perennial allergic rhinitis—a double-blind, comparative clinicopharmacological study with placebo. *J Clin Ther Med* 1997; 13:1921–39.
- 68 Numata T, Konno A, Yamakoshi T, Hanazawa T, Terada N, Nagata H. Comparative role of peptide leukotrienes and histamine in the development of nasal mucosal swelling in nasal allergy. *Ann Otol Rhinol Laryngol* 1999; 108:467–73.
- 69 Wu XQ, Myers AC, Reynolds CJ, Goldstone AC, Togias A, Sanico AM. Expression of cysteinyl leukotriene (Cys-LT) receptors 1 and 2 in the nasal mucosa in perennial allergic and non-allergic rhinosinusitis. *J Allergy Clin Immunol* 2005; 115:S56.
- 70 Meltzer EO. The prevalence and medical and economic impact of allergic rhinitis in the United States. *J Allergy Clin Immunol* 1997; 99:S805–28.
- 71 Henderson WR, Jr. The role of leukotrienes in inflammation. *Ann Intern Med* 1994; 121:684–97.
- 72 Higashi N, Taniguchi M, Mita H, Ishii T, Akiyama K. Nasal blockage and urinary leukotriene E4 concentration in patients with seasonal allergic rhinitis. *Allergy* 2003; 58:476–80.
- 73 Taylor GW, Taylor I, Black P *et al.* Urinary leukotriene E4 after antigen challenge and in acute asthma and allergic rhinitis. *Lancet* 1989; 1:584–8.
- 74 Knapp HR. Reduced allergen-induced nasal congestion and leukotriene synthesis with an orally active 5-lipoxygenase inhibitor. *N Engl J Med* 1990; 323:1745–8.
- 75 Grossman J, Ratner PH, Nathan R, Adelglass J, de Jong B. Pranlukast (ULTAIR, SB 205 312, ONO-1078), an oral leukotriene receptor antagonist, relieves symptoms in patients with seasonal allergic rhinitis (SAR). *J Allergy Clin Immunol* 1997; 99:S443.
- 76 Lim MC, Taylor RM, Naclerio RM. The histology of allergic rhinitis and its comparison to cellular changes in nasal lavage. *Am J Respir Crit Care Med* 1995; 151:136–44.
- 77 Bascom R, Wachs M, Naclerio RM, Pipkorn U, Galli SJ, Lichtenstein LM. Basophil influx occurs after nasal antigen challenge: effects of topical corticosteroid pretreatment. *J Allergy Clin Immunol* 1988; 81:580–9.
- 78 Juliusson S, Pipkorn U, Karlsson G, Enerback L. Mast cells and eosinophils in the allergic mucosal response to allergen challenge: changes in distribution and signs of activation in relation to symptoms. *J Allergy Clin Immunol* 1992; 90:898–909.
- 79 Pipkorn U, Karlsson G, Enerback L. Secretory activity of nasal mucosal mast cells and histamine release in hay fever. *Int Arch Allergy Appl Immunol* 1988; 87:349–60.
- 80 Pastorello EA, Riario-Sforza GG, Incorvaia C, Segala M, Fumagalli M, Gandini R. Comparison of rhinomanometry, symptom score, and inflammatory cell counts in assessing the nasal late-phase reaction to allergen challenge. *J Allergy Clin Immunol* 1994; 93:85–92.
- 81 Bentley AM, Jacobson MR, Cumberworth V *et al.* Immunohistology of the nasal mucosa in seasonal allergic rhinitis: increases in activated eosinophils and epithelial mast cells. *J Allergy Clin Immunol* 1992; 89:877–83.
- 82 Busse W, Kraft M. Cysteinyl leukotrienes in allergic inflammation: strategic target for therapy. *Chest* 2005; 127:1312–26.
- 83 Steinke JW, Borish L. The role of allergy in chronic rhinosinusitis. *Immunol Allergy Clin North Am* 2004; 24:45–57.
- 84 Denburg JA, Keith PK. Systemic aspects of chronic rhinosinusitis. *Immunol Allergy Clin North Am* 2004; 24:87–102.
- 85 Baatjes AJ, Sehmi R, Saito H *et al.* Anti-allergic therapies: effects on eosinophil progenitors. *Pharmacol Ther* 2002; 95:63–72.
- 86 Cyr MM, Denburg JA. Systemic aspects of allergic disease: the role of the bone marrow. *Curr Opin Immunol* 2001; 13:727–32.
- 87 Denburg JA, Otsuka H, Ohnisi M, Ruhno J, Bienenstock J, Dolovich J. Contribution of basophil/mast cell and eosinophil growth and differentiation to the allergic tissue inflammatory response. *Int Arch Allergy Appl Immunol* 1987; 82:321–6.
- 88 Denzlinger C, Kapp A, Grimberg M, Gerhartz HH, Wilmanns W. Enhanced endogenous leukotriene biosynthesis in patients treated with granulocyte-macrophage colony-stimulating factor. *Blood* 1990; 76:1765–70.
- 89 Braccioni F, Gauvreau GM, Dorman SC, Inman MD, O'Byrne PM. A leukotriene antagonist, montelukast, reduces in vitro LTD4 increases in peripheral blood eosinophil progenitor colonies in atopic subjects. Paper presented at the European Respiratory Society Annual Congress 2001, Berlin, Germany, September 22–26, 2001 [CD-ROM] Abstract 3565 Accompanied European Respiratory Journal 18(4): October 2001.

- 90 Stenke L, Mansour M, Reizenstein P, Lindgren JA. Stimulation of human myelopoiesis by leukotrienes B₄ and C₄: interactions with granulocyte-macrophage colony-stimulating factor. *Blood* 1993; **81**:352–6.
- 91 Boehmler AM, Denzlinger C, Mohle R. Cysteinyl leukotrienes are produced by human bone marrow cells and induce IL-3-dependent proliferation of CD34⁺ hematopoietic progenitors. *Blood* 2002; **100**, abstract 2873.
- 92 Saito H, Morikawa H, Howie K *et al*. Effects of a cysteinyl leukotriene receptor antagonist on eosinophil recruitment in experimental allergic rhinitis. *Immunology* 2004; **113**:246–52.
- 93 Lindgren JA, Stenke L, Mansour M *et al*. Formation and effects of leukotrienes and lipoxins in human bone marrow. *J Lipid Mediat* 1993; **6**:313–20.
- 94 Denzlinger C. Biology and pathophysiology of leukotrienes. *Crit Rev Oncol Hematol* 1996; **23**:167–223.
- 95 Ford-Hutchinson AW. Leukotriene C₄ synthase and 5-lipoxygenase activating protein. Regulators of the biosynthesis of sulfido-leukotrienes. *Ann NY Acad Sci* 1994; **744**:78–83.
- 96 Mohle R, Bautz F, Denzlinger C, Kanz L. Transendothelial migration of hematopoietic progenitor cells. Role of chemotactic factors. *Ann NY Acad Sci* 2001; **938**:26–34.
- 97 Lee BJ, Naclerio RM, Bochner BS, Taylor RM, Lim MC, Baroody FM. Nasal challenge with allergen upregulates the local expression of vascular endothelial adhesion molecules. *J Allergy Clin Immunol* 1994; **94**:1006–16.
- 98 Kanwar S, Johnston B, Kubes P. Leukotriene C₄/D₄ induces P-selectin and sialyl Lewis x dependent alterations in leukocyte kinetics *in vivo*. *Circ Res* 1995; **77**:879–87.
- 99 Pedersen KE, Bochner BS, Udem BJ. Cysteinyl leukotrienes induce P-selectin expression in human endothelial cells via a non-cysLT₁ receptor-mediated mechanism. *J Pharmacol Exp Ther* 1997; **281**:655–62.
- 100 Suzuki M, Kato M, Kimura H, Fujii T, Morikawa A. Inhibition of human eosinophil activation by a cysteinyl leukotriene receptor antagonist (pranlukast; ONO-1078). *J Asthma* 2003; **40**:395–404.
- 101 Nagata M, Saito K, Tsuchiya K, Sakamoto Y. Leukotriene D₄ upregulates eosinophil adhesion via the cysteinyl leukotriene 1 receptor. *J Allergy Clin Immunol* 2002; **109**:676–80.
- 102 Fregonese L, Silvestri M, Sabatini F, Rossi GA. Cysteinyl leukotrienes induce human eosinophil locomotion and adhesion molecule expression via a cysLT₁ receptor-mediated mechanism. *Clin Exp Allergy* 2002; **32**:745–50.
- 103 Nagata M, Sedgwick JB, Kita H, Busse WW. Granulocyte macrophage colony-stimulating factor augments ICAM-1 and VCAM-1 activation of eosinophil function. *Am J Respir Cell Mol Biol* 1998; **19**:158–66.
- 104 Laitinen LA, Laitinen A, Haahtela T, Vilkkla V, Spur BW, Lee TH. Leukotriene E₄ and granulocytic infiltration into asthmatic airways. *Lancet* 1993; **341**:989–90.
- 105 Spada C. Comparison of leukotriene B₄ and D₄ effects on human eosinophil and neutrophil motility *in vitro*. *J Leukocyte Biol* 1994; **55**:183–91.
- 106 Spada CS, Woodward DF, Hawley SB, Nieves AL. Leukotrienes cause eosinophil emigration into conjunctival tissue. *Prostaglandins* 1986; **31**:795–809.
- 107 Spada CS, Krauss AH, Nieves AL, Woodward DF. Effects of leukotrienes B₄ (LTB₄) and D₄ (LTD₄) on motility of isolated normodense human eosinophils and neutrophils. *Adv Exp Med Biol* 1997; **400B**:699–706.
- 108 Virchow JC, Jr., Faehndrich S, Nassenstein C, Bock S, Matthys H, Luttmann W. Effect of a specific cysteinyl leukotriene-receptor 1-antagonist (montelukast) on the transmigration of eosinophils across human umbilical vein endothelial cells. *Clin Exp Allergy* 2001; **31**:836–44.
- 109 Akaiwa M, Yu B, Umeshita-Suyama R *et al*. Localization of human interleukin 13 receptor in non-haematopoietic cells. *Cytokine* 2001; **13**:75–84.
- 110 Kay AB, Meng Q, Barkans J *et al*. Leukotrienes (LT) C₄, D₄, E₄ and histamine induce eotaxin expression by human endothelial cell line and human umbilical vein endothelial cells (HUVEC). *J Allergy Clin Immunol* 1999; **103**:S203.
- 111 Chibana K, Ishii Y, Asakura T, Fukuda T. Up-regulation of cysteinyl leukotriene 1 receptor by IL-13 enables human lung fibroblasts to respond to leukotriene C₄ and produce eotaxin. *J Immunol* 2003; **170**:4290–5.
- 112 Lee E, Robertson T, Smith J, Kilfeather S. Leukotriene receptor antagonists and synthesis inhibitors reverse survival in eosinophils of asthmatic individuals. *Am J Respir Crit Care Med* 2000; **161**:1881–6.
- 113 Becler K, Hakansson L, Rak S. Treatment of asthmatic patients with a cysteinyl leukotriene receptor-1 antagonist montelukast (Singulair), decreases the eosinophil survival-enhancing activity produced by peripheral blood mononuclear leukocytes *in vitro*. *Allergy* 2002; **57**:1021–8.
- 114 Evans CM, Fryer AD, Jacoby DB, Gleich GJ, Costello RW. Pretreatment with antibody to eosinophil major basic protein prevents hyperresponsiveness by protecting neuronal M₂ muscarinic receptors in antigen-challenged guinea pigs. *J Clin Invest* 1997; **100**:2254–62.
- 115 Rasp G, Thomas PA, Bujia J. Eosinophil inflammation of the nasal mucosa in allergic and non-allergic rhinitis measured by eosinophil cationic protein levels in native nasal fluid and serum. *Clin Exp Allergy* 1994; **24**:1151–6.
- 116 Wang D, Clement P, Smitz J, Derde MP. Concentrations of chemical mediators in nasal secretions of patients with hay fever during natural allergen exposure. *Acta Otolaryngol* 1994; **114**:552–5.
- 117 Tutluoglu B, Tosun GA, Akbas I, Yaman M. Effects of montelukast on serum ECP and bronchial hyperreactivity in mild asthmatics. Paper presented at the World Congress on Lung Health and 10th European Respiratory Society Annual Congress, Florence, Italy, August 30–September 3, 2000 [CD ROM] Accompanied European Respiratory Journal 17(3) 2000; Abstr.
- 118 Volovitz B, Tabachnik E, Nussinovitch M *et al*. Montelukast, a leukotriene receptor antagonist, reduces the concentration of leukotrienes in the respiratory tract of children with persistent asthma. *J Allergy Clin Immunol* 1999; **104**:1162–7.
- 119 Ohshima N, Nagase H, Koshino T *et al*. A functional study on cysLT₁ receptors in human eosinophils. *Int Arch Allergy Immunol* 2002; **129**:67–75.
- 120 Saito K, Nagata M, Kikuchi I, Sakamoto Y. Leukotriene D₄ and eosinophil transendothelial migration, superoxide generation, and degranulation via beta2 integrin. *Ann Allergy Asthma Immunol* 2004; **93**:594–600.
- 121 McComas J, Noonan G, Philip G *et al*. Safety and tolerability of montelukast in patients with seasonal allergic rhinitis: adults

- and children as young as age 2 years. *Ann Allergy Asthma Immunol* 2003; **90**:131.
- 122 Busse WW, Lemanske RF, Jr. Asthma. *N Engl J Med* 2001; **344**:350–62.
- 123 Robinson DS, Hamid Q, Ying S *et al.* Predominant TH2-like bronchoalveolar T-lymphocyte population in atopic asthma. *N Engl J Med* 1992; **326**:298–304.
- 124 Tohda Y. Effects of ONO-1078 (pranlukast) on cytokine production in peripheral blood mononuclear cells of patients with bronchial asthma. *Clin Exp Allergy* 1999; **29**:1532–6.
- 125 Bandeira-Melo C, Hall JC, Penrose JF, Weller PF. Cysteinyl leukotrienes induce IL-4 release from cord blood-derived human eosinophils. *J Allergy Clin Immunol* 2002; **109**:975–9.
- 126 Mellor EA, Austen KF, Boyce JA. Cysteinyl leukotrienes and uridine diphosphate induce cytokine generation by human mast cells through an interleukin 4-regulated pathway that is inhibited by leukotriene receptor antagonists. *J Exp Med* 2002; **195**:583–92.
- 127 Stelmach I, Jerzynska J, Kuna P. A randomized, double-blind trial of the effect of glucocorticoid, antileukotriene and β -agonist treatment on IL-10 serum levels in children with asthma. *Clin Exp Allergy* 2002; **32**:264–9.
- 128 Ciprandi G, Frati F, Marcucci F *et al.* Nasal cytokine modulation by montelukast in allergic children: a pilot study. *Allerg Immunol (Paris)* 2003; **35**:295–9.
- 129 Stelmach I, Jerzynska J, Kuna P. A randomized, double-blind trial of the effect of treatment with montelukast on bronchial hyperresponsiveness and serum eosinophilic cationic protein (ECP), soluble interleukin 2 receptor (sIL-2R), IL-4, and soluble intercellular adhesion molecule 1 (sICAM-1) in children with asthma. *J Allergy Clin Immunol* 2002; **109**:257–63.
- 130 Ichiyama T, Hasegawa S, Umeda M, Terai K, Matsubara T, Furukawa S. Pranlukast inhibits NF- κ B activation in human monocytes/macrophages and T cells. *Clin Exp Allergy* 2003; **33**:802–7.
- 131 Maspero JF, Testa M, Bezdronek L, Braillard I, Ginaca A, Kohan M. Mononuclear cell cytokine expression *in vitro* and modulation by montelukast. *J Allergy Clin Immunol* 2000; **105**:S25.
- 132 Peters-Golden M, Bailie M, Marshall T *et al.* Protection from pulmonary fibrosis in leukotriene-deficient mice. *Am J Respir Crit Care Med* 2002; **165**:229–35.
- 133 Tomari S, Matsuse H, Machida I *et al.* Pranlukast, a cysteinyl leukotriene receptor 1 antagonist, attenuates allergen-specific tumour necrosis factor alpha production and nuclear factor kappa B nuclear translocation in peripheral blood monocytes from atopic asthmatics. *J Endocrinol* 2003; **178**:37–43.
- 134 Panettieri RA, Tan EML, Ciocca V, Luttmann MA, Leonard TB, Hay DWP. Effects of LTD4 on human airway smooth muscle cell proliferation, matrix expression, and contraction *in vitro*: differential sensitivity to cysteinyl leukotriene receptor antagonists. *Am J Respir Cell Mol Biol* 1998; **19**:453–61.
- 135 Rajah R. Leukotriene D4 induces MMP-1, which functions as an IGFBP protease in human airway smooth muscle cells. *Am J Lung Cell Mol Physiol* 1996; **15**:L1014–22.
- 136 Cho SH, You HJ, Woo CH, Yoo YJ, Kim JH. Rac and protein kinase C- δ regulate ERKs and cytosolic phospholipase A2 in Fc ϵ 1 signaling to cysteinyl leukotriene synthesis in mast cells. *J Immunol* 2004; **173**:624–31.
- 137 Bloemers SM, Verheule S, Peppelenbosch MP, Smit MJ, Tertoolen LG, de Laat S. Sensitization of the histamine H1 receptor by increased ligand affinity. *J Biol Chem* 1998; **273**:2249–55.
- 138 Pynaert G. CysLTs mediate histamine hypersensitivity *ex vivo* by increasing histamine receptor numbers. *Mol Med* 1999; **10**:685–92.
- 139 Patrignani P, Modica R, Bertolero F, Patrono C. Differential effects of leukotriene C4 on endothelin-1 and prostacyclin release by cultured vascular cells. *Pharmacol Res* 1993; **27**:281–5.
- 140 Wilson AM, Dempsey OJ, Sims EJ, Lipworth BJ. A comparison of topical budesonide and oral montelukast in seasonal allergic rhinitis and asthma. *Clin Exp Allergy* 2001; **31**:616–24.
- 141 Sandrini A, Ferreira IM, Gutierrez C, Jardim JR, Zamel N, Chapman KR. Effect of montelukast on exhaled nitric oxide and nonvolatile markers of inflammation in mild asthma. *Chest* 2003; **124**:1341–9.
- 142 Bisgaard H, Loland L, Anhoj J. NO in exhaled air of asthmatic children is reduced by the leukotriene receptor antagonist montelukast. *Am J Respir Crit Care Med* 1999; **160**:1227–31.
- 143 Bratton DL, Lanz MJ, Miyazawa N, White CW, Silkoff PE. Exhaled nitric oxide before and after montelukast sodium therapy in school-age children with chronic asthma: a preliminary study. *Pediatr Pulmonol* 1999; **28**:402–7.
- 144 Larfars G, Lantoin F, Devynck MA, Palmblad J, Gyllenhammar H. Activation of nitric oxide release and oxidative metabolism by leukotrienes B4, C4, and D4 in human polymorphonuclear leukocytes. *Blood* 1999; **93**:1399–405.
- 145 Menard G, Bissonnette EY. Priming of alveolar macrophages by leukotriene D(4): potentiation of inflammation. *Am J Respir Cell Mol Biol* 2000; **23**:572–7.
- 146 Ryoyama K, Nomura T, Nakamura S. Inhibition of macrophage nitric oxide production by arachidonate-cascade inhibitors. *Cancer Immunol Immunother* 1993; **37**:385–91.
- 147 Offer S, Shoseyov D, Bibi H, Eliraz A, Madar Z. A leukotriene receptor antagonist modulates iNos in the lung and in a leukotriene-free cell model. *Nitric Oxide* 2003; **9**:10–7.
- 148 Cowburn A. 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.
- 149 Ochensberger B. Regulation of cytokine expression and leukotriene formation in human basophils by growth factors, chemokines and chemotactic agonists. *Eur J Immunol* 1999; **29**:11–22.
- 150 Lie WJ, Homburg CH, Kuijpers TW *et al.* Regulation and kinetics of platelet-activating factor and leukotriene C4 synthesis by activated human basophils. *Clin Exp Allergy* 2003; **33**:1125–34.
- 151 Silberstein DS, Owen WF, Gasson JC *et al.* Enhancement of human eosinophil cytotoxicity and leukotriene synthesis by biosynthetic (recombinant) granulocyte-macrophage colony-stimulating factor. *J Immunol* 1986; **137**:3290–4.
- 152 Scoggan KA, Ford-Hutchinson AW, Nicholson DW. Differential activation of leukotriene biosynthesis by granulocyte-macrophage colony-stimulating factor and interleukin-5 in an eosinophilic strain of HL-60 cells. *Blood* 1995; **86**:3507–16.
- 153 Brock TG, McNish RW, Coffey MJ, Ojo TC, Phare SM, Peters-Golden M. Effects of granulocyte-macrophage colony-stimulating factor on eicosanoid production by mononuclear phagocytes. *J Immunol* 1996; **156**:2522–7.

- 154 Coffey MJ, Phare SM, Cinti S, Peters-Golden M, Kazanjian PH. Granulocyte-macrophage colony-stimulating factor upregulates reduced 5-lipoxygenase metabolism in peripheral blood monocytes and neutrophils in acquired immunodeficiency syndrome. *Blood* 1999; **94**:3897–905.
- 155 Pouliot M, McDonald PP, Borgeat P, McColl SR. Granulocyte/macrophage colony-stimulating factor stimulates the expression of the 5-lipoxygenase-activating protein (FLAP) in human neutrophils. *J Exp Med* 1994; **179**:1225–32.
- 156 Thivierge M. IL-5 up-regulates cysteinyl leukotriene 1 receptor expression in HL-60 cells differentiated into eosinophils. *J Immunol* 2000; **165**:5221–6.
- 157 Espinosa K, Bosse 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.
- 158 Vargaftig BB, Singer M. Leukotrienes mediate murine bronchopulmonary hyperreactivity, inflammation, and part of mucosal metaplasia and tissue injury induced by recombinant murine interleukin-13. *Am J Respir Cell Mol Biol* 2003; **28**:410–9.
- 159 Steinke JW, Crouse CD, Bradley D *et al*. Characterization of interleukin-4-stimulated nasal polyp fibroblasts. *Am J Respir Cell Mol Biol* 2004; **30**:212–9.
- 160 Amrani Y, Moore PE, Hoffman R, Shore SA, Panettieri RA, Jr. Interferon-gamma modulates cysteinyl leukotriene receptor-1 expression and function in human airway myocytes. *Am J Respir Crit Care Med* 2001; **164**:2098–101.
- 161 Gronert K, Martinsson-Niskanen T, Ravasi S, Chiang N, Serhan CN. Selectivity of recombinant human leukotriene D(4), leukotriene B(4), and lipoxin A(4) receptors with aspirin-triggered 15-epi-LXA(4) and regulation of vascular and inflammatory responses. *Am J Pathol* 2001; **158**:3–9.
- 162 Pullerits T, Linden A, Malmhall C, Lotvall J. Effect of seasonal allergen exposure on mucosal IL-16 and CD4+ cells in patients with allergic rhinitis. *Allergy* 2001; **56**:871–7.
- 163 Bandeira-Melo C, Sugiyama K, Woods LJ *et al*. IL-16 promotes leukotriene C4 and IL-4 release from human eosinophils via CD4- and autocrine CCR3-chemokine-mediated signaling. *J Immunol* 2002; **168**:4756–63.
- 164 Steinhilber D, Radmark O, Samuelsson B. Transforming growth factor beta upregulates 5-lipoxygenase activity during myeloid cell maturation. *Proc Natl Acad Sci USA* 1993; **90**:5984–8.
- 165 Riddick CA, Serio KJ, Hodulik CR, Ring WL, Regan MS, Bigby TD. TGF-beta increases leukotriene C4 synthase expression in the monocyte-like cell line, THP-1. *J Immunol* 1999; **162**:1101–7.
- 166 Takafuji S, Bischoff SC, De Weck AL, Dahinden CA. Opposing effects of tumor necrosis factor-alpha and nerve growth factor upon leukotriene C4 production by human eosinophils triggered with N-formyl-methionyl-leucyl-phenylalanine. *Eur J Immunol* 1992; **22**:969–74.
- 167 Tamura N, Agrawal DK, Townley RG. Leukotriene C4 production from human eosinophils *in vitro*. Role of eosinophil chemotactic factors on eosinophil activation. *J Immunol* 1988; **141**:4291–7.
- 168 Kanwar S, Johnston B, Kubes P. Leukotriene C4/D4 induces P-selectin and sialyl Lewis(x)-dependent alterations in leukocyte kinetics *in vivo*. *Circ Res* 1995; **77**:879–87.
- 169 Yamamura H. Endothelin-1 induces release of histamine and leukotriene C4 from mouse bone marrow-derived mast cells. *Eur J Pharm* 1994; **257**:235–42.
- 170 Coffey MJ, Phare SM, Peters-Golden M. Interaction between nitric oxide, reactive oxygen intermediates, and peroxynitrite in the regulation of 5-lipoxygenase metabolism. *Biochim Biophys Acta* 2002; **1584**:81–90.
- 171 Gilchrist M, McCauley SD, Befus AD. Expression, localization, and regulation of NOS in human mast cell lines: effects on leukotriene production. *Blood* 2004; **104**:462–9.
- 172 Togias A. H1-receptors: localization and role in airway physiology and in immune functions. *J Allergy Clin Immunol* 2003; **112**:S60–8.
- 173 Akdis CA, Blaser K. Histamine in the immune regulation of allergic inflammation. *J Allergy Clin Immunol* 2003; **112**:15–22.
- 174 Wilson AM, O'Byrne PM, Parameswaran K. Leukotriene receptor antagonists for allergic rhinitis: a systematic review and meta-analysis. *Am J Med* 2004; **116**:338–44.
- 175 Warner JO, ETAC Study Group. A double-blinded, randomized, placebo-controlled trial of cetirizine in preventing the onset of asthma in children with atopic dermatitis: 18 months treatment and 18 months posttreatment follow-up. *J Allergy Clin Immunol* 2001; **108**:929–37.
- 176 MacGlashan DW, Jr., Schleimer RP, Peters SP *et al*. Comparative studies of human basophils and mast cells. *Fed Proc* 1983; **42**:2504–9.
- 177 Schleimer RP, Davidson DA, Peters SP, Lichtenstein LM. Inhibition of human basophil leukotriene release by antiinflammatory steroids. *Int Arch Allergy Appl Immunol* 1985; **77**:241–3.
- 178 Ochensberger B, Tassera L, Bifrare D, Rihs S, Dahinden CA. Regulation of cytokine expression and leukotriene formation in human basophils by growth factors, chemokines and chemotactic agonists. *Eur J Immunol* 1999; **29**:11–22.
- 179 Sjoström M, Jakobsson PJ, Juremalm M *et al*. Human mast cells express two leukotriene C(4) synthase isoenzymes and the cysLT(1) receptor. *Biochim Biophys Acta* 2002; **1583**:53–62.
- 180 Schleimer RP, MacGlashan DW, Jr., Peters SP, Pinckard RN, Adkinson NF, Jr., Lichtenstein LM. Characterization of inflammatory mediator release from purified human lung mast cells. *Am Rev Respir Dis* 1986; **133**:614–7.
- 181 Peters SP, MacGlashan DW, Jr., Schleimer RP, Hayes EC, Adkinson NF, Jr., Lichtenstein LM. The pharmacologic modulation of the release of arachidonic acid metabolites from purified human lung mast cells. *Am Rev Respir Dis* 1985; **132**:367–73.
- 182 Shichijo M, Inagaki N, Nakai N *et al*. The effects of anti-asthma drugs on mediator release from cultured human mast cells. *Clin Exp Allergy* 1998; **28**:1228–36.
- 183 Goldyne ME, Burrish GF, Poubelle P, Borgeat P. Arachidonic acid metabolism among human mononuclear leukocytes. Lipoxygenase-related pathways. *J Biol Chem* 1984; **259**:8815–9.
- 184 Williams JD, Czop JK, Austen KF. Release of leukotrienes by human monocytes on stimulation of their phagocytic receptor for particulate activators. *J Immunol* 1984; **132**:3034–40.
- 185 Virchow JC. Effect of a specific cysteinyl leukotriene-receptor 1-antagonist (montelukast) on the transmigration of eosinophils across human umbilical vein endothelial cells. *Clin Exp Allergy* 2001; **31**:836–44.

- 186 Weller FR. Generation and metabolism of 5-LO pathway leukotrienes by human eosinophils: predominant production of LTC₄. *Proc Natl Acad Sci USA* 1983; **80**:7626–30.
- 187 Shaw RJ, Walsh GM, Cromwell O, Moqbel R, Spry CJ, Kay AB. Activated human eosinophils generate SRS-A leukotrienes following IGG-dependent stimulation. *Nature* 1985; **316**:150–2.
- 188 Shindo K, Harai Y, Koide K, Sumitomo M, Fukumura M. In vivo effect of prednisolone on release of leukotriene C₄ in eosinophils obtained from asthmatic patients. *Biochem Biophys Res Commun* 1995; **214**:869–74.
- 189 Owen WF, Jr., Soberman RJ, Yoshimoto T, Sheffer AL, Lewis RA, Austen KF. Synthesis and release of leukotriene C₄ by human eosinophils. *J Immunol* 1987; **138**:532–8.
- 190 Hodges MK, Weller PF, Gerard NP, Ackerman SJ, Drazen JM. Heterogeneity of leukotriene C₄ production by eosinophils from asthmatic and from normal subjects. *Am Rev Respir Dis* 1988; **138**:799–804.
- 191 Harizi H, Juzan M, Pitard V, Moreau JF, Gualde N. Cyclooxygenase-2-induced prostaglandin e₂ enhances the production of endogenous IL-10, which down-regulates dendritic cell functions. *J Immunol* 2002; **168**:2255–63.
- 192 Lotzer K, Spanbroek R, Hildner M *et al.* Differential leukotriene receptor expression and calcium responses in endothelial cells and macrophages indicate 5-lipoxygenase-dependent circuits of inflammation and atherogenesis. *Arterioscler Thromb Vasc Biol* 2003; **23**:e32–6.
- 193 Spinuzzi F, Russano AM, Piattoni S *et al.* Biological effects of montelukast, a cysteinyl-leukotriene receptor-antagonist, on T lymphocytes. *Clin Exp Allergy* 2004; **34**:1876–82.
- 194 Cifone MG, Cironi L, Santoni A, Testi R. Diacylglycerol lipase activation and 5-lipoxygenase activation and translocation following TCR/CD3 triggering in T cells. *Eur J Immunol* 1995; **25**:1080–6.
- 195 Borgeat P, Samuelsson B. Arachidonic acid metabolism in polymorphonuclear leukocytes: unstable intermediate in formation of dihydroxy acids. *Proc Natl Acad Sci USA* 1979; **76**:3213–7.
- 196 McKinnon KP, Madden MC, Noah TL, Devlin RB. In vitro ozone exposure increases release of arachidonic acid products from a human bronchial epithelial cell line. *Toxicol Appl Pharmacol* 1993; **118**:215–23.
- 197 Sjoström M, Jakobsson PJ, Heimburger M, Palmblad J, Haeggström JZ. Human umbilical vein endothelial cells generate leukotriene C₄ via microsomal glutathione S-transferase type 2 and express the cysLT₁ receptor. *Eur J Biochem* 2001; **268**:2578–86.
- 198 Ramis I, Catafau JR, Serra J, Bulbena O, Picado C, Gelpi E. In vivo release of 15-HETE and other arachidonic acid metabolites in nasal secretions during early allergic reactions. *Prostaglandins* 1991; **42**:411–20.
- 199 Wang D, Clement P, Smitz J, Derde MP. Concentrations of chemical mediators in nasal secretions after nasal allergen challenges in atopic patients. *Eur Arch Otorhinolaryngol* 1995; **252**:S40–3.
- 200 Wang D, Duyck F, Smitz J, Clement P. Efficacy and onset of action of fluticasone propionate aqueous nasal spray on nasal symptoms, eosinophil count, and mediator release after nasal allergen challenge in patients with seasonal allergic rhinitis. *Allergy* 1998; **53**:375–82.
- 201 Terada N, Ando H, Ito E *et al.* Nasal allergy and leukotriene. 2. Kinetics of peptide leukotrienes and inflammatory cells in nasal lavage fluid after antigen challenge. *Nippon Jibiinkoka Gakkai Kaiho* 1989; **92**:1337–44.
- 202 Bisgaard H, Ford-Hutchinson AW, Charleson S, Taudorf E. Detection of leukotriene C₄-like immunoreactivity in tear fluid from subjects challenged with specific allergen. *Prostaglandins* 1984; **27**:369–74.
- 203 Bisgaard H, Ford-Hutchinson AW, Charleson S, Taudorf E. Production of leukotrienes in human skin and conjunctival mucosa after specific allergen challenge. *Allergy* 1985; **40**:417–23.
- 204 Konno A, Numata T, Terada N, Hanazawa T, Nagata H, Motosugi H. Role of substance P in the vascular response of nasal mucosa in nasal allergy. *Ann Otol Rhinol Laryngol* 1996; **105**:648–53.
- 205 Kojima T, Asakura K. The study of chemical mediators in the patients with allergic rhinitis. 2. Histamine, leukotriene and kinins in the nasal secretion during dual phase response. *Nippon Jibiinkoka Gakkai Kaiho* 1991; **94**:366–76.
- 206 Meltzer EO, Malmstrom K, Lu S *et al.* Concomitant montelukast and loratadine as treatment for seasonal allergic rhinitis: a randomized, placebo-controlled clinical trial. *J Allergy Clin Immunol* 2000; **105**:917–22.