LEUKOTRIENES (“LEUKO,” FROM WHITE BLOOD CELLS; AND “TRIENES,” THREE conjugated double bonds) comprise a family of products of the 5-lipoxygenase pathway of arachidonic acid metabolism. The cysteinyl leukotrienes C₄, D₄, and E₄ account for the biologic activity that was previously termed “slow-reacting substance of anaphylaxis,” and the efficacy of antagonists to type 1 cysteinyl leukotriene receptor (CysLT₁) in asthma validates the importance of cysteinyl leukotrienes and CysLT₁ in this disease.¹ This article reviews both established understanding and recent advances in our knowledge about leukotrienes.

SYNTHESIS OF LEUKOTRIENES

The synthesis of leukotrienes from substrate arachidonic acid is initiated by 5-lipoxygenase in concert with 5-lipoxygenase–activating protein (FLAP)² (Fig. 1). Although FLAP does not have enzymatic activity, it enhances the ability of 5-lipoxygenase to interact with its substrate. Leukotriene A₄ (LTA₄) is converted by LTA₄ hydrolase to leukotriene B₄ (LTB₄), or it can be conjugated with reduced glutathione by leukotriene C₄ (LTC₄) synthase to yield LTC₄. LTB₄ and LTC₄ are exported from the cell by specific transporter proteins; the released LTC₄ is converted to leukotriene D₄ (LTD₄), which undergoes conversion to leukotriene E₄ (LTE₄) by sequential amino acid hydrolysis. The capacity to generate large amounts of leukotrienes from arachidonate is largely confined to leukocytes; however, the amounts of LTB₄ and cysteinyl leukotrienes that various types of leukocytes produce depend on the distal enzymes LTA₄ hydrolase and LTC₄ synthase, respectively (Table 1 and Glossary).

Although nonleukocyte cells generally do not have sufficient 5-lipoxygenase and FLAP to synthesize appreciable amounts of leukotrienes from arachidonate, such cells expressing distal LTA₄-metabolizing enzymes can take up leukocyte-derived LTA₄ and metabolize it into bioactive leukotrienes, a process that is termed “transcellular bio- synthesis.”³ The interaction between neutrophils and endothelial cells is an example of this phenomenon: a neutrophil (the donor cell) containing 5-lipoxygenase provides LTA₄ to the endothelial cell (the acceptor cell), which lacks 5-lipoxygenase but expresses LTC₄ synthase and can thereby metabolize the donated LTA₄ to LTC₄. Products of the 5-lipoxygenase pathway besides leukotrienes (5-hydroxyeicosatetraenoic acid, 5-oxo-eicosatetraenoic acid,⁴ and lipoxins⁵) are not considered in this review.

The output of the leukotriene synthetic pathway is regulated by the amount of free arachidonate that phospholipase A₂ releases from cell-membrane phospholipids,⁶ the level of each of the proteins in the 5-lipoxygenase pathway, the catalytic activity per enzyme molecule (e.g., modulated by protein kinase–directed phosphorylation⁷), and the availability of small molecules (e.g., ATP, nitric oxide,⁸ and reactive oxygen intermediates) that modulate 5-lipoxygenase activity.

Another variable that influences leukotriene synthesis is the intracellular localization of 5-lipoxygenase. In resting leukocytes, this enzyme can reside in the cytoplasm or the nucleoplasm, and it shuttles between them by regulated nuclear import and

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Leukotrienes

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export processes. When 5-lipoxygenase is activated, it relocates to the outer or inner nuclear membrane. The movement of 5-lipoxygenase from the nucleoplasm to the inner nuclear membrane is associated with a maximal synthesis of LTB₄.

Heritable deficiencies of enzymes in the leukotriene synthetic pathway are rare, but there are allelic variants of the coding and promoter regions of the genes for 5-lipoxygenase, FLAP, hydrolase, and LTC₄ synthase. Moreover, the transcription of these genes can be regulated by cytokines, transforming growth factor β, leptin, endothelin, vitamin D₃, endotoxin, and corticosteroids. Expression of LTC₄ synthase, for example, is up-regulated by interleukin-4 and down-regulated by endotoxin.

LEUKOTRIENE RECEPTORS

Leukotrienes act by binding to specific heptahelical receptors of the rhodopsin class that are located on the outer plasma membrane of structural and inflammatory cells. Once ligated by the leukotriene, these receptors interact with G proteins in the cytoplasm, thereby eliciting increases in intracellular calcium and reductions in intracellular cyclic AMP. These proximal signals activate downstream kinase cascades in ways that alter various cellular activities, ranging from motility to transcriptional activation. Table 1 lists the major types of cells that express leukotriene receptors.

Type 1 cysteinyl leukotriene receptor (CysLT₁) mediates sustained bronchoconstriction, mucus secretion, and edema in the airways. Selective antagonists of CysLT₁ that are approved for the treatment of asthma block the proasthmatic effects of CysLT₁ (Fig. 1). Experiments in mice that are deficient in type 2 cysteinyl leukotriene receptor (CysLT₂) or that overexpress CysLT₁ in the lungs indicate that CysLT₂ does not mediate bronchoconstriction but, rather, contributes to inflammation, vascular permeability, and tissue fibrosis. There are no known specific antagonists of CysLT₂. Certain reported actions of cysteinyl leukotrienes are not readily explained by either

<table>
<thead>
<tr>
<th>Glossary</th>
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<tbody>
<tr>
<td><strong>BLT₁</strong></td>
</tr>
<tr>
<td><strong>BLT₂</strong></td>
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<tr>
<td><strong>CysLT₁</strong></td>
</tr>
<tr>
<td><strong>CysLT₂</strong></td>
</tr>
<tr>
<td><strong>Cysteinyl leukotrienes</strong></td>
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<tr>
<td><strong>5-Lipoxygenase</strong></td>
</tr>
<tr>
<td><strong>FLAP</strong></td>
</tr>
<tr>
<td><strong>LTA₄</strong></td>
</tr>
<tr>
<td><strong>LTA₄ hydrolase</strong></td>
</tr>
<tr>
<td><strong>LTB₄</strong></td>
</tr>
<tr>
<td><strong>LTC₄</strong></td>
</tr>
<tr>
<td><strong>LTC₄ synthase</strong></td>
</tr>
<tr>
<td><strong>LTD₄</strong></td>
</tr>
<tr>
<td><strong>LTE₄</strong></td>
</tr>
<tr>
<td><strong>Rhodopsin</strong></td>
</tr>
</tbody>
</table>
CysLT₁ or CysLT₂, raising the possibility of the presence of CysLT₁–CysLT₂ heterodimers or additional receptors.²³ One candidate is G protein–coupled receptor 17 (GPR17), a dual-uracil nucleotide–cysteinyl leukotriene receptor.²⁶ B leukotriene receptor 1 (BLT₁) is the high-affinity receptor for LTB₄ that mediates most, if not all, of its chemoattractant and proinflammatory action.²⁰ B leukotriene receptor 2 (BLT₂) is a lower-affinity receptor for LTB₄ that also binds other lipoxygenase products; little is known about its physiological function.

The expression of CysLT₁ can be influenced at the transcriptional level by type 2 helper T (Th2)-cell–type cytokines.²⁷ This effect probably explains why CysLT₁ is overexpressed in patients with asthma or chronic rhinosinusitis who have aspirin sensitivity and why levels of the receptor return to normal after aspirin desensitization.²⁸ In addition to the actions of cysteinyl leukotrienes in the airway, they join LTB₄ in exerting other biologic actions. Some of the actions of cysteinyl leukotrienes and LTB₄ are distinctive (e.g., smooth-muscle contraction for the former and

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**Figure 1. Leukotriene Synthesis, Receptors, and Signaling.**

Leukotriene synthesis can be activated in a cell (e.g., a leukocyte) by a variety of stimuli. The enzymatic machinery for phospholipase A₂ (PLA₂)–catalyzed arachidonate hydrolysis and leukotriene synthesis is localized primarily at or near the nuclear membrane, necessitating that leukotriene B₄ (LTB₄) and leukotriene C₄ (LTC₄) be transported by carrier proteins out of the cell; the LTC₄ transporter is multidrug resistance protein 1; the LTB₄ transporter is unknown. In the extracellular milieu, LTC₄ is converted to leukotriene D₄ (LTD₄) and LTD₄ to leukotriene E₄ (LTE₄). Collectively, these molecules make up the cysteinyl leukotrienes. Leukotrienes act on target cells, which may be leukocytes, epithelial cells, smooth-muscle cells, or endothelial cells, by interacting with one or both classes of their cognate receptors. B leukotriene receptor 1 (BLT₁) is expressed primarily on leukocytes and is a high-affinity receptor, whereas B leukotriene receptor 2 (BLT₂) is expressed more ubiquitously, has a somewhat lower affinity for LTB₄, and can bind other lipids. The two cysteinyl leukotriene receptors have a broad distribution. All leukotriene receptors activate the Gq class of G proteins, resulting in increased intracellular calcium, the Gi class, resulting in decreased intracellular cyclic AMP (cAMP), or both. These effects, which activate downstream protein kinases, culminate in myriad cellular and tissue responses. The sites of action of antileukotriene drugs (5-lipoxygenase [5-LO] for zileuton and CysLT₁ for montelukast, zafirlukast, and pranlukast) are shown. FLAP denotes 5-lipoxygenase–activating protein.
neutrophil chemotaxis for the latter), whereas other actions (e.g., promotion of allergic responses) are not. Leukotrienes promote the movement into tissues and function of virtually all subgroups of leukocytes29-32 (Fig. 2). Also important is their role in amplifying inflammatory responses mediated by Th2 cells.33-35 The ability of a CysLT₁ antagonist to reduce serum levels of IgE in children with asthma is indicative of the effects of cysteinyl leukotrienes on systemic immune responses.36

### Blockade of Leukotriene Synthesis and Leukotriene Receptors

Commonly used antiinflammatory medications do not predictably interfere with the synthesis of 37 or responses to38 leukotrienes. Nonsteroidal antiinflammatory drugs can actually increase the production of leukotrienes,39 and corticosteroids can increase the expression of BLT₁ on neutrophils.40 CysLT₁ antagonists (Fig. 1) include montelukast, zafirlukast, and pranlukast (the last available only in Japan). The only other antileukotriene drug that has been approved by the Food and Drug Administration (FDA) is zileuton, which directly inhibits 5-lipoxygenase; this effect blocks production of cysteinyl leukotrienes and LT₄. Zileuton inhibits an estimated 26 to 86% of endogenous leukotriene production.41 The clinical use of zileuton is limited by the need to monitor hepatic enzyme levels and to administer the drug four times daily. A twice-daily sustained-release form of zileuton has recently received FDA approval. Other candidate 5-lipoxygenase inhibitors also have hepatotoxicity. The hepatic injury caused by zileuton appears to be a direct toxic effect that is unrelated to inhibition of 5-lipoxygenase.42

An alternative way of blocking leukotriene synthesis is to inhibit FLAP. The crystal structure of this molecule has recently been reported,43 and this information should prove useful in drug design. One FLAP inhibitor, DG031 (velifulapon, DeCode Genetics), is being reformulated for use in phase 3 trials for the prevention of myocardial infarction. Selective BLT₁ antagonists that have been developed up to now have been tested in animal models of disease,44 but none have emerged for clinical use.

## Leukotrienes in Disease

Leukotrienes have a multitude of biologic actions (Table 2) and have been suggested as factors in numerous disease processes (Table 3). The role of leukotrienes has been validated in clinical trials of antileukotriene agents for asthma and only a few of the other diseases listed in Table 3.

### Asthma

#### Antileukotriene Drugs as Controller Agents

The benefits of antileukotriene therapy (i.e., 5-lipoxygenase inhibition by zileuton45 and CysLT₁ blockade by montelukast or zafirlukast46-47) in children and adults with asthma are improved pulmonary function, decreased daytime and nocturnal symptoms, a reduced need for short-acting rescue β₂ agonists, fewer exacerbations of asthma, and an increased quality of life. Inhaled corticosteroids are more potent than antileukotriene agents48 and hence are favored as first-line treatment; however, antileukotriene therapy can be used initially in a patient who cannot or will not take corticosteroids.49 Antileukotriene agents have an additive benefit in patients whose disease is not adequately controlled by inhaled corticosteroids,50 perhaps reflecting the inability of corticosteroids

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**Table 1. Leukotriene Synthesis and Receptor Expression in Leukocyte Subgroups.**

<table>
<thead>
<tr>
<th>Type of Cell</th>
<th>Relative Synthetic Capacity</th>
<th>Receptor Expression</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LTB₄ Cysteinyl Leukotrienes</td>
<td>BLT₁ CysLT₁ CysLT₂</td>
</tr>
<tr>
<td>Neutrophil</td>
<td>+++</td>
<td>− + ±</td>
</tr>
<tr>
<td>Macrophage or monocyte</td>
<td>++ +</td>
<td>+ + ±</td>
</tr>
<tr>
<td>Eosinophil</td>
<td>− +++</td>
<td>+ + +</td>
</tr>
<tr>
<td>Basophil</td>
<td>− +++</td>
<td>+ + +</td>
</tr>
<tr>
<td>Mast cell</td>
<td>+ +++</td>
<td>+ + +</td>
</tr>
<tr>
<td>B lymphocyte</td>
<td>− − ND</td>
<td>+ + ND</td>
</tr>
<tr>
<td>CD8 T lymphocyte</td>
<td>− − ND</td>
<td>+ + ND</td>
</tr>
<tr>
<td>CD8 T lymphocyte</td>
<td>− − ND</td>
<td>+ + ND</td>
</tr>
<tr>
<td>Hematopoietic progenitor cell</td>
<td>− − ND</td>
<td>+ + ND</td>
</tr>
</tbody>
</table>

* Relative synthetic capacity is expressed by the number of plus (+) signs; a minus sign (−) denotes no or negligible synthetic capacity. Receptor expression is classified as positive (+), negative (−), minimal (±), or not determined (ND). With respect to cells for which discrepancies exist in reports on leukotriene synthesis or receptor expression, the table lists the best available information taken from primary cells, particularly those that are human in origin.
Figure 2. Leukocyte Recruitment and Activation by Leukotrienes.
By ligating their specific cognate receptors (which are summarized in Table 1), leukotrienes promote the accumulation and function of virtually all subgroups of leukocytes at sites of inflammation. Such responses are important in the pathogenesis of diseases, including asthma, cardiovascular disease, and cancer. Leukotrienes affect leukocytes by stimulating the growth of bone marrow CD34+ pluripotent hematopoietic stem-cell progenitors and their subsequent migration into the bloodstream. Leukotrienes also increase the expression of adhesion proteins (thereby enhancing leukocyte adhesion to the microvasculature) and promote cell motility, which leads to transmigration into tissues. Once leukocytes reach the inflamed tissues, their survival and activation are enhanced by leukotrienes. Through BLT1 leukotriene receptor 1 (BLT1), leukotriene B4 (LTB4) primarily mediates the recruitment of mast cells, neutrophils, monocytes or macrophages, and T cells; through type 1 cysteinyl leukotriene receptor (CysLT1), cysteinyl leukotrienes, including leukotriene D4 (LTD4), promote the recruitment of eosinophils, dendritic cells, and T cells.
to inhibit leukotriene pathways. Although the weight of evidence from randomized, controlled studies indicates that antileukotriene agents are inferior to long-acting β2 agonists as add-on therapy to inhaled corticosteroids (particularly with respect to improving lung function), some studies have shown that montelukast is similar to long-acting β2 agonists in reducing symptoms and exacerbations of asthma.

Some patients with asthma are particularly good candidates for antileukotriene therapy. One example is the patient with allergic rhinitis. The nasal congestion and rhinorrhea in allergic rhinitis are reduced by montelukast to a degree similar to that with antihistamines but inferior to that with topical corticosteroids. Since allergic rhinitis is often present with asthma and complicates its management, a leukotriene modifier could improve upper- and lower-airway symptoms and signs. However, trials of the use of montelukast to reduce the need for other rhinitis medications in patients with both asthma and allergic rhinitis have had divergent results.

Montelukast also provides protection against exercise-induced asthma. A single oral dose of montelukast is as effective as inhaled salmeterol, a long-acting β2 agonist, in preventing exercise-induced asthma, and its regular use during a 2-month period was not associated with the development of tachyphylaxis, as occurs with the use of salmeterol.

Antileukotriene agents are beneficial in patients with aspirin-sensitive asthma, a condition in which production of very high levels of cysteinyl leukotrienes is typical. However, even among such patients, the drugs are inconsistent in their abil-

### Table 2. Effects of Leukotrienes on the Biologic Actions of Cells Associated with Asthma, Cardiovascular Disease, and Cancer.

<table>
<thead>
<tr>
<th>Type of Cell</th>
<th>Asthma</th>
<th>Cardiovascular Disease</th>
<th>Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukocyte</td>
<td>Increases recruitment of T cells, eosinophils, and mast cells</td>
<td>Increases monocyte and T-cell recruitment</td>
<td>Increases recruitment of monocytes</td>
</tr>
<tr>
<td></td>
<td>Increases Th2 responses, cytokines or chemokines, and reactive oxygen species</td>
<td>Increases differentiation of macrophages or foam cells</td>
<td>Increases cytokines or chemokines and reactive oxygen species</td>
</tr>
<tr>
<td>Endothelial cell</td>
<td>Increases vascular permeability</td>
<td>Increases vascular permeability and angiogenesis</td>
<td></td>
</tr>
<tr>
<td>Smooth-muscle cell</td>
<td>Increases contractility and proliferation</td>
<td>Increases contractility and proliferation</td>
<td></td>
</tr>
<tr>
<td>Fibroblast or myofibroblast</td>
<td>Increases collagen release</td>
<td>Increases vascular permeability and angiogenesis</td>
<td></td>
</tr>
<tr>
<td>Dendritic cell</td>
<td>Increases cell recruitment and activation</td>
<td>Increases intimal hyperplasia</td>
<td></td>
</tr>
<tr>
<td>Epithelial cell</td>
<td>Increases mucus release and goblet cells</td>
<td>Increases chemokines (e.g., MCP-1 and MIP-1α) and proteases</td>
<td></td>
</tr>
<tr>
<td>Malignant cell</td>
<td>NA</td>
<td>Increases proliferation (e.g., kinase or β-catenin signaling)</td>
<td>Increases expression of adhesion molecules</td>
</tr>
<tr>
<td></td>
<td>NA</td>
<td>Increases transcriptional activity of oncogenic genes</td>
<td>Decreases apoptosis (by increasing Bcl-2) to increase tumor-cell survival</td>
</tr>
</tbody>
</table>

*Th2 denotes type 2 helper T cell, MCP-1 monocyte chemoattractant protein 1, MIP-1α macrophage inflammatory protein 1α, MIP-2 macrophage inflammatory protein 2, and NA not applicable.
† Biologic action is most closely attributable to both leukotriene B4 and cysteinyl leukotrienes.
‡ Biologic action is most closely attributable to leukotriene B4.
§ Biologic action is most closely attributable to cysteinyl leukotrienes.
ity to attenuate responses to aspirin challenge. Applications of antileukotriene therapy that remain under investigation are the treatment of persistent respiratory symptoms in children after respiratory syncytial virus infection and the treatment of acute asthma exacerbations in children and adults.

**Effects of Antileukotriene Agents on Airway Remodeling**

Structural alterations referred to as “airway remodeling,” consisting of increases in the number of airway goblet cells and smooth-muscle mass, as well as deposition of subepithelial collagen (Table 2), contribute to the progressive loss of lung function in patients with chronic asthma. For this reason, a desirable feature of controller therapy for asthma is its ability to ameliorate airway remodeling. Airway remodeling appears to be resistant to inhaled corticosteroids. However, in a mouse model of chronic allergic asthma, CysLT1 blockade with montelukast reversed all of the histologic features of airway remodeling. Myofibroblasts, which are mesenchymal cells with features of both fibroblasts and smooth-muscle cells, have been implicated in airway remodeling because of their high capacity for collagen synthesis. In atopic asthma, the allergen-induced increase in the number of myofibroblasts in the airway wall is limited by montelukast treatment, but whether antileukotriene drugs prevent or ameliorate airway remodeling in patients with asthma is unknown.

**Responsiveness to Antileukotriene Agents**

Since asthma involves multiple mediators, it is not surprising that the efficacy of agents that target only components of the 5-lipoxygenase pathway is limited and variable. Why are antileukotriene drugs effective in some patients and ineffective in others?

One explanation for the efficacy of these drugs is that CysLT1 signaling contributes to many aspects of asthma pathogenesis besides constriction of bronchial smooth muscle. For example, CysLT1 influences systemic immune responses and has bidirectional interactions with cytokines. The interplay between the Th2 cytokine interleukin-13 and cysteinyl leukotrienes and CysLT1 exemplifies such relationships (Fig. 3). Variations in responses of patients with asthma to corticosteroids and β2 agonists were illuminated by studies of an antileukotriene agent. In randomized, controlled trials with these drugs,

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### Table 3. Diseases That Have a Possible Association with Leukotrienes.

<table>
<thead>
<tr>
<th>Allergic diseases</th>
<th>Asthma*</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Allergic rhinitis*</td>
</tr>
<tr>
<td></td>
<td>Rhinosinusitis</td>
</tr>
<tr>
<td></td>
<td>Atopic dermatitis†</td>
</tr>
<tr>
<td></td>
<td>Urticaria†</td>
</tr>
<tr>
<td>Fibrotic diseases</td>
<td>Airway remodeling in asthma</td>
</tr>
<tr>
<td></td>
<td>Bronchiolitis obliterans after lung transplantation</td>
</tr>
<tr>
<td></td>
<td>Idiopathic pulmonary fibrosis‡</td>
</tr>
<tr>
<td></td>
<td>Scleroderma</td>
</tr>
<tr>
<td></td>
<td>Asbestosis</td>
</tr>
<tr>
<td>Other pulmonary syndromes</td>
<td>Acute lung injury or adult respiratory distress syndrome</td>
</tr>
<tr>
<td></td>
<td>Viral bronchiolitis†</td>
</tr>
<tr>
<td></td>
<td>Obstructive sleep apnea†</td>
</tr>
<tr>
<td></td>
<td>Chronic obstructive pulmonary disease‡ †</td>
</tr>
<tr>
<td></td>
<td>Cystic fibrosis§ and other forms of bronchiectasis</td>
</tr>
<tr>
<td></td>
<td>Bronchopulmonary dysplasia</td>
</tr>
<tr>
<td>Other local inflammatory diseases</td>
<td>Arthritis (including osteoarthritis and gout)</td>
</tr>
<tr>
<td></td>
<td>Glomerulonephritis</td>
</tr>
<tr>
<td></td>
<td>Interstitial cystitis†</td>
</tr>
<tr>
<td></td>
<td>Psoriasis</td>
</tr>
<tr>
<td></td>
<td>Inflammatory bowel disease¶</td>
</tr>
<tr>
<td>Systemic inflammatory diseases</td>
<td>Rheumatoid arthritis†</td>
</tr>
<tr>
<td></td>
<td>Vasculitides (systemic lupus erythematosus,† Churg-Strauss syndrome, Henoch-Schonlein purpura)</td>
</tr>
<tr>
<td></td>
<td>Transplant rejection</td>
</tr>
<tr>
<td>Cancer</td>
<td>Solid tumors (including melanoma, mesothelioma, and pancreatic, lung,‡ esophageal, prostate, and colon cancers)</td>
</tr>
<tr>
<td></td>
<td>Leukemias</td>
</tr>
<tr>
<td></td>
<td>Lymphomas</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>Atherosclerosis†</td>
</tr>
<tr>
<td></td>
<td>Aortic aneurysm</td>
</tr>
<tr>
<td></td>
<td>Sickle cell crisis</td>
</tr>
<tr>
<td></td>
<td>Ischemia–reperfusion injury</td>
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<tr>
<td></td>
<td>Pulmonary arterial hypertension</td>
</tr>
<tr>
<td></td>
<td>Sepsis</td>
</tr>
</tbody>
</table>

* An association has been established in large-scale randomized, double-blind, placebo-controlled clinical trials, and the Food and Drug Administration has approved an antileukotriene intervention.
† An association has been established in small-scale or nonrandomized, placebo-controlled trials indicating that leukotrienes may play a role in disease pathogenesis, but larger randomized clinical trials are required.
‡ Clinical trials are ongoing or contemplated.
§ Adverse events (e.g., increased infectious exacerbations) that were associated with antileukotriene therapy have been reported.
¶ Results of a clinical trial involving patients with ulcerative colitis were negative.
symptoms were reduced as compared with baseline in 60 to 80% of patients, whereas improvements in lung function were noted in only 35 to 50% of such patients. This discordance in outcome measures may be due to differences among patients in leukotriene biology, genotype, or clinical characteristics.

After spontaneous episodes of bronchospasm in patients with asthma or after challenge with allergen, exercise, or aspirin in susceptible patients, levels of cysteinyl leukotrienes increase in airway fluids and urine. Urinary LTE₄, a measure of whole-body synthesis of cysteinyl leukotrienes, is a possible predictor of drug responsiveness, and significant associations between high urinary LTE₄ levels and responsiveness to antileukotriene agents have been reported. Other studies, however, have shown either no such relationship or an inverse relationship. It seems that technical limitations and spontaneous variations in the level of urinary LTE₄ reduce its value as a robust predictor of the response to antileukotriene therapy in individual patients. Leukotriene synthesis by cultured leukocytes is also an unreliable predictor of the clinical response to pranlukast.

In patients with asthma who were treated with a 5-lipoxygenase inhibitor, polymorphisms in the promoter of the 5-lipoxygenase gene (ALOX5) were associated with diminished improvement in airflow. However, since these genetic variants occur in less than 10% of patients with asthma, they can explain only a fraction of the unresponsiveness to leukotriene modifiers. By contrast, an A-to-C transversion in the LTC₄ synthase promoter region occurs in approximately 20 to 40% of patients with asthma and is associated with increased synthesis of cysteinyl leukotrienes. A positive relation between this variant allele and the clinical response to various CysLT₁ antagonists was reported in two studies but not in a third. A variant allele in the coding region of the gene encoding CysLT₂ has recently been reported to be associated with an enhanced response to montelukast. It is likely that these pharmacogenetic associations vary according to the geographic origin of the population under analysis. Since levels of leukotrienes and their receptors are greatly influenced by substances such as cytokines, analysis of responsiveness to antileukotriene therapy must take into account the genes for
Improvements to antileukotriene drugs. A benefit is more likely in children than in adults and in younger children than in older children. Moreover, acquired factors such as obesity and smoking may be relevant in understanding the clinical effects of antileukotriene agents. Although in one study the effect of inhaled beclomethasone on asthma control declined with increasing body-mass index, no such decline was observed for montelukast, suggesting that the relative benefit of montelukast may have been greater in more obese patients. Likewise, patients with asthma who smoked had a greater response to montelukast than did their nonsmoking counterparts.

**Therapeutic Trials of Antileukotriene Agents**

Since it is impossible to predict responsiveness to antileukotriene therapy in an individual patient, a therapeutic trial in the patient may be necessary. Improvements in symptoms or a reduced need for rescue bronchodilators can be seen with antileukotriene therapy as early as the first day of treatment, since cysteiny1 leukotrienes increase bronchial tone. Reductions in levels of exhaled nitric oxide and bronchial hyperresponsiveness occur within 1 week and 2 weeks after the initiation of therapy, respectively, and improvements in lung function and symptoms occur over a period of weeks or months. A trial period of 1 to 2 months is recommended.

Montelukast is the most commonly used inhibitor of the leukotriene pathway because of its ease of use, good safety profile, and once-daily regimen. However, use of this CysLT1 antagonist ignores possible contributions of CysLT2 to effects mediated by cysteiny1 leukotrienes. Montelukast also does not inhibit other products of the 5-lipoxygenase pathway — most notably, LTB4. The lack of an effect on LTB4 could be important, because this leukocyte chemoattractant and activator is probably involved in severe asthma and asthma exacerbations. A 5-lipoxygenase inhibitor might therefore have better efficacy than a CysLT1 antagonist. Although retrospective data support the possibility that zileuton is more effective in severe asthma than in mild asthma, there are no data from large-scale, prospective comparisons of an inhibitor of leukotriene synthesis with a CysLT1 antagonist.

**Cardiovascular Disease**

The role of leukotrienes in cardiovascular disease has been the subject of intense investigation (Tables 2 and 3). Atherosclerotic vascular lesions express the entire cassette of leukotriene biosynthetic proteins (5-lipoxygenase, FLAP, LTA4 hydrolase, and LTC4 synthase) and receptors (CysLT1, CysLT2, BLT1, and BLT2). Moreover, levels of 5-lipoxygenase correlate with the severity of the atherosclerotic lesion and plaque instability. Studies in animals and in vitro suggest that both LTB4 and cysteine1 leukotrienes participate in the development of atherosclerotic lesions. LTB4, by promoting BLT1-mediated intracellular signaling, contributes to recruitment of monocytes and foam-cell differentiation, as well as intimal hyperplasia. Cysteine1 leukotrienes — probably involving signaling mediated by both CysLT1 and CysLT2 — enhance the recruitment of leukocytes into the arterial wall and contribute to thrombosis and vascular remodeling (Fig. 2 and Table 2).

The incidence of strokes and myocardial infarctions in European, Japanese, and American black populations has been linked to variants of the genes that encode FLAP and LTA4 hydrolase; these variants result in overproduction of leukotrienes. In a 4-week pilot study, Icelandic patients with a history of myocardial infarction and one of the variant genes that encodes FLAP or LTA4 hydrolase who were treated with the investigational FLAP inhibitor DG031 (veliflapon) had a significant reduction in levels of C-reactive protein, a biomarker of inflammation that has been linked to cardiovascular disease. In a population of predominantly white North Americans, the association of variants of the FLAP gene with cardiovascular disease is less clear. Two studies in the United States showed no association between variants of FLAP and the risk of ischemic stroke and one of the studies also showed no association between these alleles and myocardial infarction. Another U.S.-based study showed an association between FLAP variants and ischemic strokes among whites but not blacks.

Other polymorphisms involving the 5-lipoxygenase pathway have been linked to atherosclerotic...
sis. In women, an A-to-C transversion in the LTC₄ synthase promoter region has been associated with an age-adjusted risk of increased levels of coronary-artery calcium and an increased mean intimal–medial thickness of the carotid artery,₄⁰ a surrogate measure of atherosclerosis. Carotid intimal–medial thickness was also shown to be increased in carriers of two variant alleles of the 5-lipoxygenase promoter in a North American population.⁵⁰ The same 5-lipoxygenase promoter polymorphisms were not associated with an increased risk of myocardial infarction in a Spanish population.⁶⁰ Taken together, these data suggest a role of leukotrienes in the development of atherosclerotic vascular disease, and genetic studies suggest a population-specific influence of polymorphisms in genes encoding leukotriene biosynthetic enzymes or leukotriene receptors.

**CANCER**

Chronic inflammation can increase the risk of cancer. Cysteinyl leukotrienes and LTB₄ that are released by inflammatory cells infiltrating the mucosa of the gut in inflammatory bowel disease may be mediators of such malignant transformation (Table 2). LTD₄ activates β-catenin signaling, leading to the up-regulation of the antiapoptotic protein Bel-2 and increased cell survival.⁶⁷ As compared with normal intestinal epithelial cells, colorectal adenocarcinomas have increased nuclear localization of CysLT₁, which may facilitate proliferation of the malignant cells by kinase signaling.⁷⁰ LTB₄ signaling has also been associated with cancer-cell proliferation. In colon-cancer tissue and cell lines, there is increased expression of BLT₁, and when BLT₁ is suppressed in cultured cells by a small interfering RNA, cell proliferation decreases.⁷⁹

Malignant cells in colorectal, esophageal, and pancreatic adenocarcinomas, bronchogenic carcinoma, melanoma, lymphomas, and leukemias express large amounts of 5-lipoxygenase, FLAP, and other leukotriene biosynthetic enzymes.⁸⁰,⁸¹ In one study, treatment of 5-lipoxygenase–expressing esophageal cancer cell lines with a 5-lipoxygenase inhibitor decreased cell survival.⁸² The effects of the inhibitor paralleled reductions in LTB₄ production and could be reversed by exogenous LTB₄, which indicated that the decreased cell survival was due to interruption of LTB₄ synthesis. Chronic lymphocytic leukemia cells express large amounts of 5-lipoxygenase and BLT₁, and treatment with an investigational inhibitor of 5-lipoxygenase or FLAP blocks the CD40-dependent activation of these cells; this effect is reversed by the addition of LTB₄ to the cultured cells.¹¹³

In a mouse model of lung cancer, a FLAP inhibitor that reduces leukotriene synthesis reduced the volume of lung tumors induced by a tobacco-specific carcinogen.¹¹⁴ In rats with a gastroesophageal reflux disease similar to Barrett’s esophagus, an esophageal adenocarcinoma that overexpresses LTA₄ hydrolase developed; inhibition of LTB₄ synthesis by the LTA₄ hydrolase inhibitor bestatin reduced the incidence and volume of such tumors.¹¹⁵ Administration of both zileuton and bestatin also reduced the incidence of carcinogen-induced oral squamous-cell carcinoma in hamsters.¹¹⁶ These results are the basis of an ongoing clinical trial sponsored by the National Cancer Institute to test the idea that interruption of leukotriene synthetic pathways or leukotriene receptors reduces the growth of cancer.¹¹⁴

**LEUKOTRIENES IN ANTIMICROBIAL DEFENSE**

Leukotrienes that are synthesized in response to a spectrum of infectious agents enhance the capacities of macrophages and neutrophils to ingest and kill microbes and to produce antimicrobial mediators.¹¹⁷ LTB₄–BLT₁ signaling exerts broader and more potent effects in this regard than does signaling between cysteinyl leukotrienes and CysLT₁. In animal models of infection, genetic or pharmacologic interruption of leukotriene synthesis or signaling impairs local microbial clearance.¹¹⁷ For example, lungs of 5-lipoxygenase–null mice contain almost 100 times as much Klebsiella pneumoniae as do lungs of wild-type animals 48 hours after intrapulmonary bacterial inoculation.

In humans, acquired states of leukotriene deficiency have been described in human immunodeficiency virus (HIV) infection¹¹⁸ and protein-calorie malnutrition.¹¹⁹ In HIV infection, leukotriene deficiency is the result of reduced expression of 5-lipoxygenase and, especially, of FLAP. These reductions are a consequence of a deficiency of CD4 T-cell–derived cytokines that stimulate the production of these elements in the leukotriene pathway.¹²⁰ Although patients with asthma who are treated with antileukotriene agents do not have an increased risk of infection, a significant in-
crease in the risk of infectious pulmonary exacerbations was reported in patients with cystic fibrosis who were treated with an investigational BLT1 antagonist (BIIL 284), necessitating early termination of the clinical trial.120

CONCLUSIONS

Today, nearly three decades since leukotrienes were discovered and one decade since drugs targeting this pathway became available, new and often unexpected insights into the biology and clinical importance of these lipid mediators continue to emerge. Beyond the classically recognized and validated participation of cysteinyl leukotrienes in asthma, it is now evident that leukotrienes are multifunctional mediators that influence many biologic responses and probably play a role in other diseases.

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