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Invited review article

The role of leukotrienes in allergic diseases

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ABSTRACT

Leukotrienes (LTs), both LTB_4 and the cysteinyl LTs (CysLTs) LTC_4, LTD_4 and LTE_4, are implicated in a wide variety of inflammatory disorders. These lipid mediators are generated from arachidonic acid via multistep enzymatic reactions through which arachidonic acid is liberated from membrane phospholipids through the action of phospholipase A_2. LTB_4 and CysLTs exert their biological effects by binding to cognate receptors, which belong to the G protein-coupled receptor superfamily. LTB_4 is widely considered to be a potent chemoattractant for most subsets of leukocytes, whereas CysLTs are potent bronchoconstrictors that have effects on airway remodeling. LTs play a central role in the pathogenesis of asthma and many other inflammatory diseases. This review will provide an update on the synthesis, biological function, and relevance of LTs to the pathobiology of allergic diseases, and examine the current and future therapeutic prospects of LT modifiers.

Introduction

In addition to their primary role as a source of nutrients, lipids are the major components of cell membranes. Lipid derivatives such as prostaglandins (PGs) and leukotrienes (LTs) function as signaling molecules and play pivotal roles in inflammatory and immune responses. LTs are divided into two classes, namely, the chemoattractant LTB_4, which only carries hydroxyl moieties, and the cysteinyl LTs [CysLTs: LTC_4, LTD_4, and LTE_4],[1,2] which also carry amino acid moieties. LTs are generated from arachidonic acid via the 5-lipoxygenase (5-LO) pathway and are representative lipid mediators or bioactive lipids. LTs exert their biological effects by binding to G protein-coupled receptors (GPCRs).[3] Different LT receptor subtypes exert unique functions.[4] LTs are involved in various inflammatory diseases, including asthma, allergic rhinitis, atopic dermatitis, allergic conjunctivitis, rheumatoid arthritis, chronic obstructive pulmonary disease, obliterative bronchiolitis after lung transplantation, and interstitial lung diseases.[5] This review provides an overview of recent findings related to the synthesis of LTs and their cognate receptors, examines their relevance to the pathobiology of allergic diseases, and discusses both current and future therapeutic prospects.

Overview of the 5-LO pathway

Arachidonic acid is released from the sn-2 position of membrane phospholipids by phospholipase A_2 in response to various biological stimuli[6,7] and subsequently metabolized by the cyclooxygenase (COX) and lipoxygenase (LO) pathways to generate PGs and LTs, respectively.[8] There are at least six different types of mammalian lipoxygenase, which are named according to the carbon position at which a single oxygen molecule is incorporated. Among them, 5-LO, expressed mainly in granulocytes, macrophages and mast cells, is the most widely studied one.[9] Arachidonic acid is first oxidized at the C-5 position by the dual enzymatic activity of 5-LO to yield 5-hydroxyperoxyeicosatetraenoic acid (5-HpETE) followed by an unstable intermediate, leukotriene A_4 (LTA_4); 5-HpETE acts in concert with 5-LO-activating protein (FLAP) in a Ca^{2+} dependent manner.[10,11] LTA_4 is either converted to LTB_4 by LTA_4 hydrolase[12–16] or conjugated to reduced glutathione by leukotriene C_4 synthase (LTC_4S) to yield CysLT (LTC_4).[17–19] LTC_4 is then exported from the cell and converted to LTD_4 and LTE_4, the most stable CysLTs, by extracellular peptidases (Fig. 1). A transcellular mechanism that generates CysLTs has also been reported.[20] Cells containing 5-LO, but not LTC_4S (e.g., neutrophils), release LTA_4, which is then used by other cells that express LTC_4S but not 5-LO (e.g., platelets or endothelial cells). This mechanism of transcellular biosynthesis is important for generating high concentrations of CysLTs in the local environment.

Studies of mouse models of different inflammatory diseases, such as platelet-activating factor (PAF)-induced shock, arachidonic

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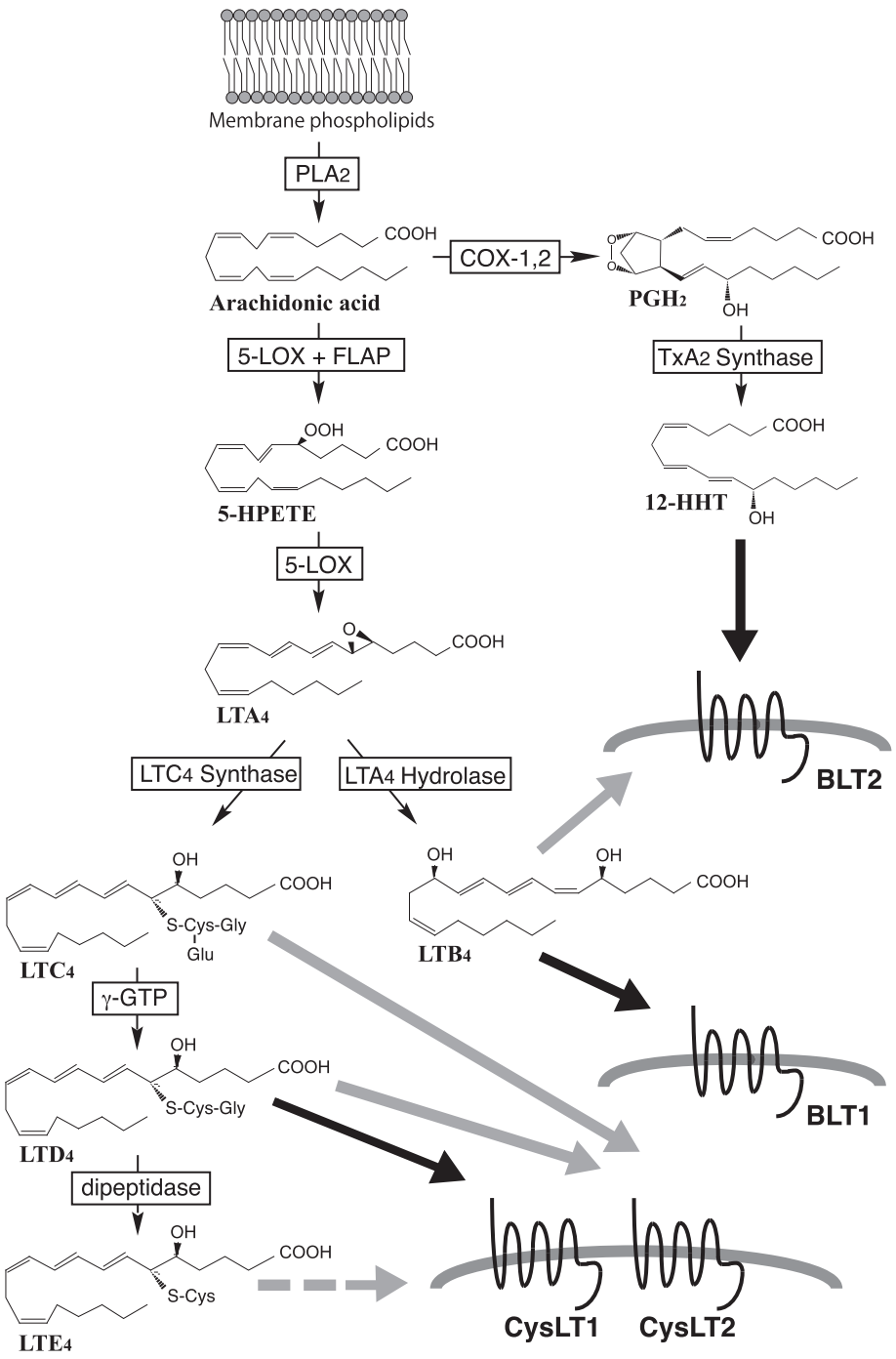

Fig. 1. The arachidonic acid cascade generates leukotrienes from membrane phospholipids. PLA_2, phospholipase A_2; COX, cyclooxygenase; 5-LOX, 5-lipoxygenase; FLAP, 5-lipoxygenase activating protein; 5-HPETE, 5-hydroperoxyeicosatetraenoic acid. The names of the enzymes are given in the boxes.

acid-induced ear edema, glycogen- and zymosan-induced peritonitis, and ovalbumin-induced airway inflammation, show that mice deficient in 5-LO are unable to synthesize detectable levels of LTs and thus display reduced levels of inflammation.[21–24] Mice deficient in LTA_4 hydrolase, which is required for the production of LTB_4, show similarly reduced responses after the induction of zymosan-induced peritonitis and PAF-induced shock.[25]

A competitive inhibitor of the 5-LO enzyme, zileuton, the only agent that can inhibit the production of LT, has been approved for the treatment of asthma.[26–31] Recent studies report that a nM LTC_4S inhibitor, the synthesis of which was based on the crystal structure of the enzyme, shows potential for future drug development.[32,33] Finally, FLAP inhibitors (MK-886, MK-0591, BAY X1005, and DG-031) have been developed and appear to show promise.[34–39]

LTB_4 and its receptors

LTB_4 was first identified as a potent mediator of leukocyte function by Ford-Hutchinson and colleagues,[40] who showed that it was chemotactic for neutrophils, and this finding was further confirmed by Palmer et al.[41] Nowadays, LTB_4 is widely considered