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Eicosanoid Lipid Mediators in Fibrotic Lung Diseases*

Ready for Prime Time?

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Recognition of a pivotal role for eicosanoids in both normal and pathologic fibroproliferation is long overdue. These lipid mediators have the ability to regulate all cell types and nearly all pathways relevant to fibrotic lung disorders. Abnormal fibroproliferation is characterized by an excess of profibrotic leukotrienes and a deficiency of antifibrotic prostaglandins. The relevance of an eicosanoid imbalance is pertinent to diseases involving the parenchymal, airway, and vascular compartments of the lung, and is supported by studies conducted both in humans and animal models. Given the lack of effective alternatives, and the existing and emerging options for therapeutic targeting of eicosanoids, such treatments are ready for prime time.

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Key words: airway remodeling; leukotrienes; prostaglandins; pulmonary fibrosis

Abbreviations: cAMP = cyclic adenosine monophosphate; cysLT = cysteinyl leukotriene; COX = cyclooxygenase; cysLT1 = cysteinyl leukotriene receptor 1; EP = E prostanoid receptor; IL = interleukin; IP = I prostanoid receptor; IPF = idiopathic pulmonary fibrosis; 5-LO = 5-lipoxygenase; LT = leukotriene; PG = prostaglandin; TGF = transforming growth factor; Th = T helper

As a result of both research advances and therapeutic disappointments over the past 20 years, favored concepts regarding the pathobiology of pulmonary fibrosis have shifted from a central focus on inflammation to one of abnormal fibroproliferative responses to lung injury that result in tissue remodeling.[1] Such responses are thought to involve the apoptotic loss of alveolar epithelial cells; recruitment, expansion, and activation of mesenchymal cells; and deposition of excess matrix proteins such as collagen, particularly by α-smooth muscle actin-positive myofibroblasts. These processes in turn are driven by a profibrotic milieu that is characterized by oxidant stress, growth factors such as transforming growth factor (TGF)-β, T-helper (Th) type 2 immune response polarization, and abnormalities in the coagulation cascade.[1] Although the prototypic fibroproliferative lung diseases are diffuse disorders of the pulmonary parenchyma, such as idiopathic pulmonary fibrosis (IPF), many aspects of their pathobiology are shared by remodeling diseases involving other compartments of the lung. Examples include airway remodeling in patients with asthma and bronchiolitis obliterans, and vascular remodeling in patients with pulmonary arterial hypertension. Unfortunately, advances in the understanding of the pathobiology of IPF have not yet been translated into effective therapies, and its prognosis remains exceedingly poor.[2]

This review focuses on one particular class of mediators that has been implicated in fibrotic lung

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disorders; namely, eicosanoid metabolites of arachidonic acid, which include leukotrienes (LTs) and prostaglandins (PGs). Because of either unawareness or bias on the part of investigators and thought leaders, the participation of eicosanoids is certainly underappreciated and often entirely unmentioned in review articles or scientific symposia concerning fibrogenesis. The following three features of eicosanoids in this context deserve attention and will be emphasized herein: (1) remodeling disorders of the lung are characterized by an imbalance favoring profibrotic LTs over antifibrotic PGs; (2) the eicosanoid imbalance hypothesis provides a framework that integrates and helps to explain the effects of many other mediators and modifying influences; and (3) therapeutic targeting of eicosanoids, already well-established in diseases such as asthma and pulmonary hypertension and rapidly advancing in sophistication, provides opportunities for application to fibrotic lung disease.

Eicosanoids: Synthesis and Cellular Effects

Eicosanoids are a group of lipid mediators derived from the 20-carbon fatty acid arachidonic acid (*eicosa* is Greek for "20"). After release from membrane phospholipids by cytosolic phospholipase A_2 (Fig 1), arachidonate is further metabolized by the 5-lipoxygenase (5-LO) pathway into LTs or by the cyclooxygenase (COX)-1/COX-2 pathway into PGs.[3] LTs include both LTB_4 and the cysteinyl LTs (cysLTs) C_4, D_4, and E_4, and are synthesized mainly by leukocytes. PGs, including PGE_2, PGI_2, PGD_2, $PGF_2\alpha$, and thromboxane A_2, are synthesized by both leukocytes and structural cells. Individual cell types generate specific profiles of eicosanoids that reflect their complement of terminal synthase enzymes. LTs and PGs exert a myriad of actions that contribute to both homeostasis and disease. Eicosanoids act in a paracrine or autocrine fashion by ligating specific 7-transmembrane G protein-coupled

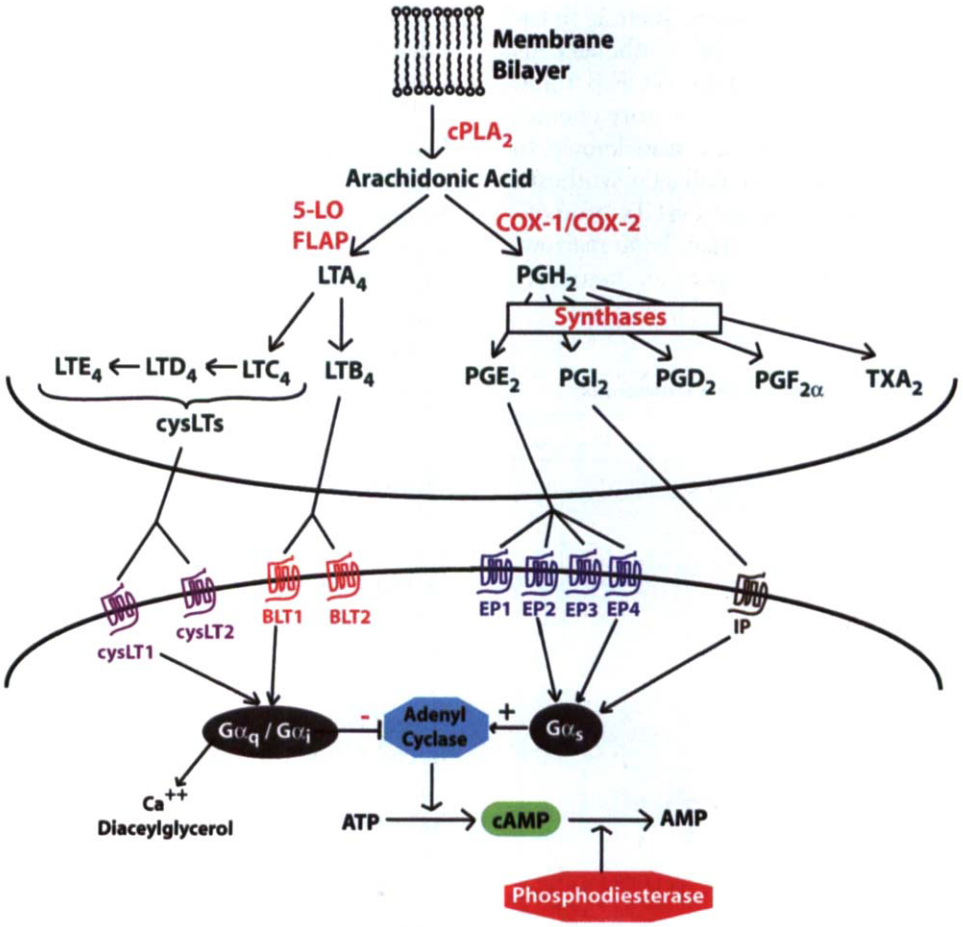

FIGURE 1. Eicosanoid synthesis and receptors. Arachidonic acid, released from membrane phospholipids by cytosolic phospholipase A_2 ($cPLA_2$), can be metabolized by the 5-LO pathway to make LTs or by the COX pathway to make PGs. Terminal synthases complete the biosynthesis of specific eicosanoid products. Eicosanoids exert their actions via binding to 7-transmembrane G-protein-coupled receptors and subsequent intracellular signaling. FLAP = 5-LO activating protein; ATP = adenosine triphosphate; AMP = adenosine monophosphate; TXA_2 = thromboxane A_2.