

Update on the role of prostaglandins in allergic lung inflammation: Separating friends from foes, harder than you might think

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Prostaglandins (PGs), small lipid molecules derived from arachidonic acid by COX enzymes, are critical mediators of allergic inflammation. Our understanding of the role of PGs in allergic lung inflammation has been hampered by the very short biologic half-life of these mediators, which has made mechanistic studies difficult in human subjects. However, advances in molecular biology and pharmacology have given investigators the opportunity to examine the role of specific prostanooids in the development of allergic inflammation in animal models. Studies investigating specific PG receptors are also elucidating the mechanisms by which PGs regulate the pulmonary allergic phenotype. This review summarizes the current literature on the role of PGs and PG receptors in allergic lung inflammation. (J Allergy Clin Immunol 2006;117:1036-9.)

Key words: Allergy, prostaglandins

PROSTAGLANDINS IN ALLERGIC LUNG INFLAMMATION

The synthesis, metabolism, and signaling of the 5 major prostaglandins (PGs; PGD₂, PGE₂, PGF_{2α}, PGI₂, and thromboxane A₂ [TXA₂]) are tightly regulated by cell type-specific and PG-specific pathways. Two COX enzyme isoforms, COX-1 and COX-2, convert arachidonic acid liberated from the membrane phospholipids to an unstable PGG₂ intermediate by a COX activity and then convert PGG₂ to PGH₂ by an endoperoxidase activity (Fig 1).¹ Arachidonic acid can also be metabolized by 5-lipoxygenase for synthesis of leukotrienes (Fig 1). Both COX-1 and COX-2 are expressed in the respiratory epithelium and in inflammatory cells in the lung. COX-1 is expressed constitutively, whereas COX-2 expression

Abbreviations used

BALF: Bronchoalveolar lavage fluid
cAMP: Cyclic AMP
DC: Dendritic cell
OVA: Ovalbumin
PG: Prostaglandin
TXA₂: Thromboxane A₂

is induced in inflammation. Induction of COX-2 in antigen-presenting cells, such as macrophages and dendritic cells (DCs), is thought to be important for PG production in the setting of allergic lung inflammation. Specific PG synthases convert PGH₂ to PGD₂, PGE₂, PGF_{2α}, PGI₂, or TXA₂ (Fig 1). The regulation of expression of the PG synthases, although not well defined, is thought to be an important determinant of the profile of PGs produced by cells. PGs bind specific G protein-coupled receptors (Fig 1) and can mediate their effects in an autocrine manner, a paracrine manner, or both. As discussed below, PG receptors are key modulators of allergic lung inflammation, and recent studies with PG receptor gene knockout mice are providing new insights into the complex role of PGs in the pathogenesis of allergic lung inflammation.

The murine (eg, mouse and rat) ovalbumin (OVA) model has been used extensively to investigate immune mechanisms of allergic lung inflammation. In this model animals are sensitized to OVA typically by means of 1 or 2 intraperitoneal injections of an OVA-aluminum hydroxide solution, and the mice are then challenged approximately 2 weeks later with repeated exposures to a nebulized solution of OVA. The resulting allergic inflammation is characterized by increased levels of PGs, increased concentrations of T_H2 cytokines (IL-4, IL-5, and IL-13) in the lung, influx of eosinophils and lymphocytes in the bronchoalveolar lavage fluid (BALF), mucus production, and increased airway reactivity. The functions of OVA peptide-presenting DCs and OVA-specific T cells and the interaction of these 2 cell types at the interface of innate and adaptive immunity are central to pathogenesis in the murine OVA model.

The importance of PGs for the pathogenesis of allergic lung inflammation has been established by preventing the formation of these lipid mediators. Allergen sensitization

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Disclosure of potential conflict of interest: The authors have declared that they have no conflict of interest.

Received for publication September 12, 2005; revised November 2, 2005; accepted for publication December 8, 2005.

Available online February 15, 2006.

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0091-6749/\$32.00

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doi:10.1016/j.jaci.2005.12.1314

and challenge of mice deficient in COX-1² or mice treated with a selective COX-1 antagonist, a selective COX-2, or the nonselective COX inhibitor indomethacin^{3,4} results in augmented allergic inflammation with T_H2 cytokine production and airway reactivity. The increased allergic inflammation that occurs as a result of treatment with a nonselective COX inhibitor is independent of signaling through IL-4, the IL-4 receptor α , or signal transducer and activation of transcription (STAT) 6 signaling.⁵ Therefore inhibiting PG formation results in increased allergic inflammation, suggesting that the overall effect of PGs during the allergen sensitization and challenge process is to restrain allergic inflammation. However, individual prostanoids might either augment or inhibit allergic inflammation, depending on the specific receptor through which they signal. The general current paradigm is that PGD₂, PGF_{2 α} , and TXA₂ increase allergic inflammation, whereas PGE₂ and PGI₂ inhibit the allergen-induced inflammatory response. Recent studies, reviewed below, support this paradigm and provide mechanistic clues and potential therapeutic targets for allergic airway inflammation.

PGD₂ AND RECEPTORS DP AND CRTH2

In allergic lung inflammation PGD₂ activates eosinophils, is a potent bronchoconstrictor, and promotes vascular permeability, thereby contributing to pathogenesis. In the mouse OVA model overexpression of the human lipocalin-type PGD synthase (L-PGDS) gene in the lung resulted in increased PGD₂ levels, increased numbers of eosinophils and lymphocytes in the BALF, and increased BALF levels of IL-4 and IL-5.⁶ Similarly, pretreatment of OVA-sensitized mice with aerosolized PGD₂ 1 day before challenge with a low dose of aerosolized OVA resulted in increased numbers of eosinophils, lymphocytes, and macrophages in the BALF and increased levels of IL-4 and IL-5.⁷ These results suggest that PGD₂ promotes pulmonary allergic inflammation.

Two receptors for PGD₂ have been identified, DP and CRTH2. DP is expressed in eosinophils, antigen-presenting cells, and basophils, and CRTH2 is expressed in eosinophils, T_H2 cells, and basophils. In the OVA model DP gene knockout mice (DP^{-/-}) exhibited decreased numbers of eosinophils and lymphocytes in the BALF and decreased BALF concentrations of IL-4, IL-5, and IL-13.⁸ Because the inability to signal through DP reduced allergic inflammation, these results suggest that signaling through DP heightens the allergic phenotype. In support of the notion that DP signaling is pro-inflammatory, uteroglobin, an anti-inflammatory protein secreted by epithelial cells, blocked DP signaling and reduced T_H2 cytokine levels and eosinophilia in the mouse OVA model.⁹ In human subjects a variant of the DP gene (PTGDR) was associated with lower levels of DP gene transcription, and US populations with at least one copy of this haplotype had lower risk of asthma compared with those with no copies of this haplotype.¹⁰ CRTH2, an alternative PGD₂ receptor, was identified when a DP

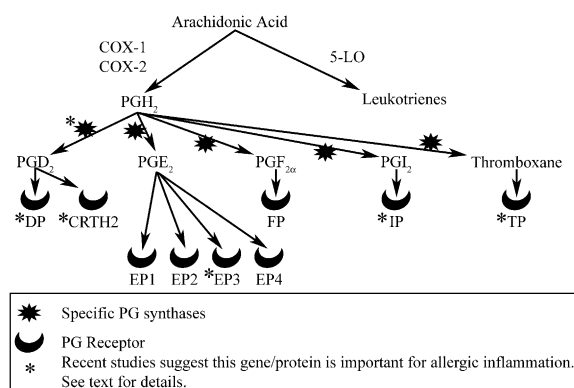


FIG 1. A schematic of the pathways of arachidonic acid metabolism that leads to prostaglandin and leukotriene synthesis and the prostaglandin receptors are shown. 5-LO, 5-Lipoxygenase.

agonist did not stimulate eosinophil migration *in vitro*, suggesting that signaling through this receptor might also promote allergic inflammatory responses.¹¹ CRTH2 agonists increased eosinophilia and pathology in the mouse OVA model, and the CRTH2/TP antagonist ramatroban inhibited PGD₂-mediated eosinophilia.^{12,13} Paradoxically, though, CRTH2^{-/-} mice exhibited increased eosinophilia in the OVA model.¹⁴ These authors hypothesize that CRTH2 signaling might increase eosinophil recruitment early in allergic lung inflammation and then restrain it at later time points.¹⁴

PGE₂ AND RECEPTORS EP1, EP2, EP3, AND EP4

In allergic lung inflammation and allergic asthma, PGE₂ is produced by the airway epithelium, smooth muscle, DCs, and macrophages. *In vivo* studies, both in human subjects and in animals, suggest that PGE₂ inhibits allergic responses in the lung. In allergic asthmatic subjects inhaled PGE₂ administered immediately before inhaled allergen challenge significantly reduced the immediate-phase decrease in FEV₁, the late-phase decrease in FEV₁, and methacholine responsiveness 24 hours after allergen challenge.¹⁵ In addition, inhaled PGE₂ inhibited the number of allergen-induced eosinophils and metachromatic cells in sputum both 7 and 24 hours after allergen challenge.¹⁵ In another study of atopic asthmatic subjects, inhaled PGE₂ before endobronchial allergen challenge resulted in decreased eosinophils and PGD₂ in the BALF, again suggesting that PGE₂ restrains allergic inflammation.¹⁶ Inhaled PGE₂ also reduced T_H2 cytokine production and cysteinyl leukotriene generation in BALF in the rat model of OVA-induced allergic inflammation.¹⁷ PGE₂ can have pleiotropic effects on inflammation that are likely due, in part, to the contextual expression of the 4 known PGE₂ receptors, EP1, EP2, EP3, and EP4, which have specific cell-signaling functions. Signaling through the EP1 receptor results in mobilization of intracellular calcium stores. In contrast, EP2 and EP4 are coupled to

G proteins that stimulate pathways resulting in increased concentration of intracellular cyclic AMP (cAMP). Signaling through the EP3 receptor is not well defined, although EP3 stimulation can decrease cAMP concentration. There are several isoforms of EP3 representing alternative splice variants of the EP3 mRNA. *In vitro*, EP1 and EP3 signaling generally opposes EP2 and EP4 signaling. EP3-deficient, but not EP1-, EP2-, or EP4-deficient, mice exhibit enhanced allergic inflammation in the mouse OVA model, and the selective EP3 agonist AE-248 suppressed the augmented inflammation.¹⁸ These results suggest that signaling through EP3 is responsible for the ability of PGE₂ to downregulate allergic inflammation.

PGE₂ has also been implicated in the pathogenesis of aspirin-induced asthma. Inhaled PGE₂ inhibited aspirin-induced airway constriction in subjects with aspirin-sensitive asthma.¹⁹ The mechanism by which PGE₂ blocks the effect of aspirin in aspirin-sensitive subjects is likely multifactorial. Signaling through EP3, PGE₂ prevents acetylcholine release from parasympathetic nerve endings.²⁰ Bronchial fibroblasts from aspirin-sensitive subjects might produce decreased levels of PGE₂ compared with those seen in nonasthmatic subjects or subjects with aspirin-tolerant asthma, perhaps offering one mechanism by which subjects with aspirin-sensitive asthma are different from other subjects with asthma.²¹ In addition, PGE₂ inhibits aspirin-induced increases in urinary leukotriene E₄ in aspirin-sensitive subjects, and persons with aspirin-induced asthma have greater airways responsiveness to the cysteinyl leukotrienes than subjects with non-aspirin-sensitive asthma.¹⁹ Persons with aspirin-sensitive asthma have greater numbers of leukocytes expressing the cysteinyl leukotriene receptor compared with subjects who are not aspirin, another possible mechanism by which sensitivity to aspirin might be increased in this patient population.²²

PGI₂ AND RECEPTOR IP

Studies examining signaling through the PGI₂ receptor IP support the hypothesis that PGI₂ plays a protective role in allergic lung inflammation. IP is expressed by a variety of cell types, including T cells, mast cells, basophils, endothelial cells, and vascular smooth muscle cells. Signaling through the IP receptor can increase cAMP concentration. Increased cAMP concentration in T cells is associated with decreased effector function. In the OVA model IP^{-/-} mice had exacerbated airway inflammation, eosinophilia, and increased serum OVA-specific and total IgE levels compared with those seen in control mice.²³ These results therefore suggest that PGI₂ signaling through IP suppresses the allergic phenotype. One potential mechanism by which PGI₂ inhibits allergic inflammation is through increasing T-cell production of IL-10, a cytokine known to suppress T_H2 immunity. PGI₂ analog treatment of OVA-specific T lymphocytes stimulated with an OVA peptide had no effect on IL-4, IL-5, or IL-13 production, yet IL-10 protein expression was increased.³

TXA₂ AND RECEPTOR TP

TXA₂, a PG produced mainly by platelets, is a bronchoconstrictor, promotes platelet aggregation, and stimulates acetylcholine release. New evidence suggests that TXA₂ plays an important role in allergic lung inflammation. In human subjects polymorphisms in the TP gene (TBXAR2) are associated with asthma and atopy.^{24,25} In mice both a thromboxane synthase inhibitor and a thromboxane receptor antagonist independently reduced allergen-induced airway eosinophilia.²⁶ In a guinea pig OVA model in which OVA-sensitized and OVA-challenged animals are given a low dose of indomethacin to roughly equilibrate lung levels of leukotrienes and TXA₂, a dual antagonist (YM158) for TP and the cysteinyl leukotriene receptor 1 inhibited OVA-induced airway resistance to a greater extent than either a specific TP antagonist (seratrodast) or a specific cysteinyl leukotriene receptor 1 antagonist (pranlukast).²⁷ These authors propose that targeting TXA₂ and leukotrienes simultaneously is a good strategy because patients might exhibit a leukotriene- or TXA₂-dominant asthma phenotype.²⁷ TP-deficient mice have been generated, but the phenotype of these mice in the OVA model has not been reported.

SUMMARY: DELINEATING THE ROLE OF PGs IN ALLERGIC LUNG INFLAMMATION

PGs clearly play an important role in the development and maintenance of allergic inflammation in the lung. Studies investigating the PG receptors are elucidating the roles of specific PG-PG receptor interactions in the immunoregulation and pathophysiology of allergic lung inflammation. As reviewed, current *in vivo* animal studies suggest that PGD₂ and TXA₂ both increase allergic phenotype, whereas PGE₂ and PGI₂ restrain the allergen-induced inflammatory response. Our increased knowledge of PG receptor biology provides mechanistic insight into the complex biology of PGs in allergic lung inflammation and also provides therapeutic targets, particularly PG receptors themselves, for treatment of allergic lung diseases, such as allergic asthma. Future studies aimed at elucidating factors that regulate PG receptor and PG synthase expression, as well as PG signaling pathways, will provide a more complete picture of the role of PGs in allergic lung inflammation.

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