

Role of lipid mediators and control of lymphocyte responses in type 2 immunopathology



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Type 2 immunopathology is a cardinal feature of allergic diseases and involves cooperation between adaptive immunity and innate effector responses. Virtually all cell types relevant to this pathology generate leukotriene and/or prostaglandin mediators that derive from arachidonic acid, express receptors for such mediators, or both. Recent studies highlight prominent functions for these mediators in communication between the innate and adaptive immune systems, as well as amplification or suppression of type 2 effector responses. This review focuses on recent advances and insights, and highlights existing and potential therapeutic applications of drugs that target these mediators or their receptors, with a special emphasis on their regulation of the innate and adaptive lymphocytes relevant to type 2 immunopathology. (*J Allergy Clin Immunol* 2018;141:1182-90.)

Key words: Innate type 2 immunopathology, allergic inflammation, asthma, eosinophilic esophagitis, aspirin-exacerbated respiratory disease, innate lymphoid cells, innate immune cells, eicosanoids, cysteinyl leukotrienes, prostaglandins, prostacyclins

Asthma, eosinophilic esophagitis (EoE), and chronic rhinosinusitis have become markedly more common in Western societies in the past half century. These diseases all involve end-organ dysfunction caused by persistent activation of the immune system, resulting in eosinophil-rich (type 2) immunopathology. Because these diseases cause substantial morbidity, developing new therapeutics and preventive strategies is a high priority. Such development requires an in-depth understanding of the underlying molecular and cellular mechanisms.

Abbreviations used

AA:	Arachidonic acid
AERD:	Aspirin-exacerbated respiratory disease
BAL:	Bronchoalveolar lavage
CRTH2:	Chemoattractant receptor-homologous molecule expressed on T _H 2 cells
cysLT:	Cysteinyl leukotriene
CysLT ₁ R:	Cysteinyl leukotriene receptor type 1
CysLT ₂ R:	Cysteinyl leukotriene receptor type 2
CysLT ₃ R:	Cysteinyl leukotriene receptor type 3
DC:	Dendritic cell
DP:	D prostanoïd
EoE:	Eosinophilic esophagitis
EP:	E-prostanoid receptor
EpC:	Epithelial cell
GPCR:	G protein-coupled receptor
5-HETE:	5-Hydroxytetraenoic acid
hPGDS:	Hematopoietic prostaglandin D synthase
ILC2:	Group 2 innate lymphoid cell
IP:	I prostanoïd
5-LO:	5-Lipoxygenase
LT:	Leukotriene
LTC ₄ S:	Leukotriene C ₄ synthase
LX:	Lipoxin
mPGES-1:	Microsomal prostaglandin E ₂ synthase 1
OVA:	Ovalbumin
PG:	Prostaglandin
TSLP:	Thymic stromal lymphopoietin
TX:	Thromboxane
WT:	Wild-type

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Supported by National Institutes of Health grants AI078908, AI095219, AT002782, AI082369, HL111113, and HL117945 and by generous contributions from the Vinik Family.

Disclosure of potential conflict of interest: The authors declare that they have no relevant conflicts of interest.

Received for publication December 22, 2017; revised February 8, 2018; accepted for publication February 9, 2018.

Available online March 2, 2018.

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0091-6749/\$36.00

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<https://doi.org/10.1016/j.jaci.2018.02.006>

Allergic diseases involve prominent contributions from both the innate and adaptive immune systems. Thymic stromal lymphopoietin (TSLP), IL-25, and IL-33 are generated primarily by barrier epithelial cells (EpCs) and released in the innate response to pathogens, antigens, and local injury (Fig 1). Their expression can also be persistently upregulated with severe disease, resulting in sustained pathology. Of their target cells, group 2 innate lymphoid cells (ILC2s) generate especially large quantities of type 2 cytokines (IL-5, IL-13, and IL-9)¹⁻³ when stimulated with barrier-derived cytokines,⁴ as do mast cells, basophils, and certain populations of T_H2 cells. In mouse models of helminth infection, ILC2s are sufficient to induce mucosal eosinophilia and goblet cell hyperplasia, even in mice lacking adaptive immune systems.⁵ Although less is known about the role of ILC2s in human disease, recent studies implicate ILC2s as potentially important sources of type 2 cytokines in patients with asthma, chronic rhinosinusitis, and EoE.⁶⁻⁸

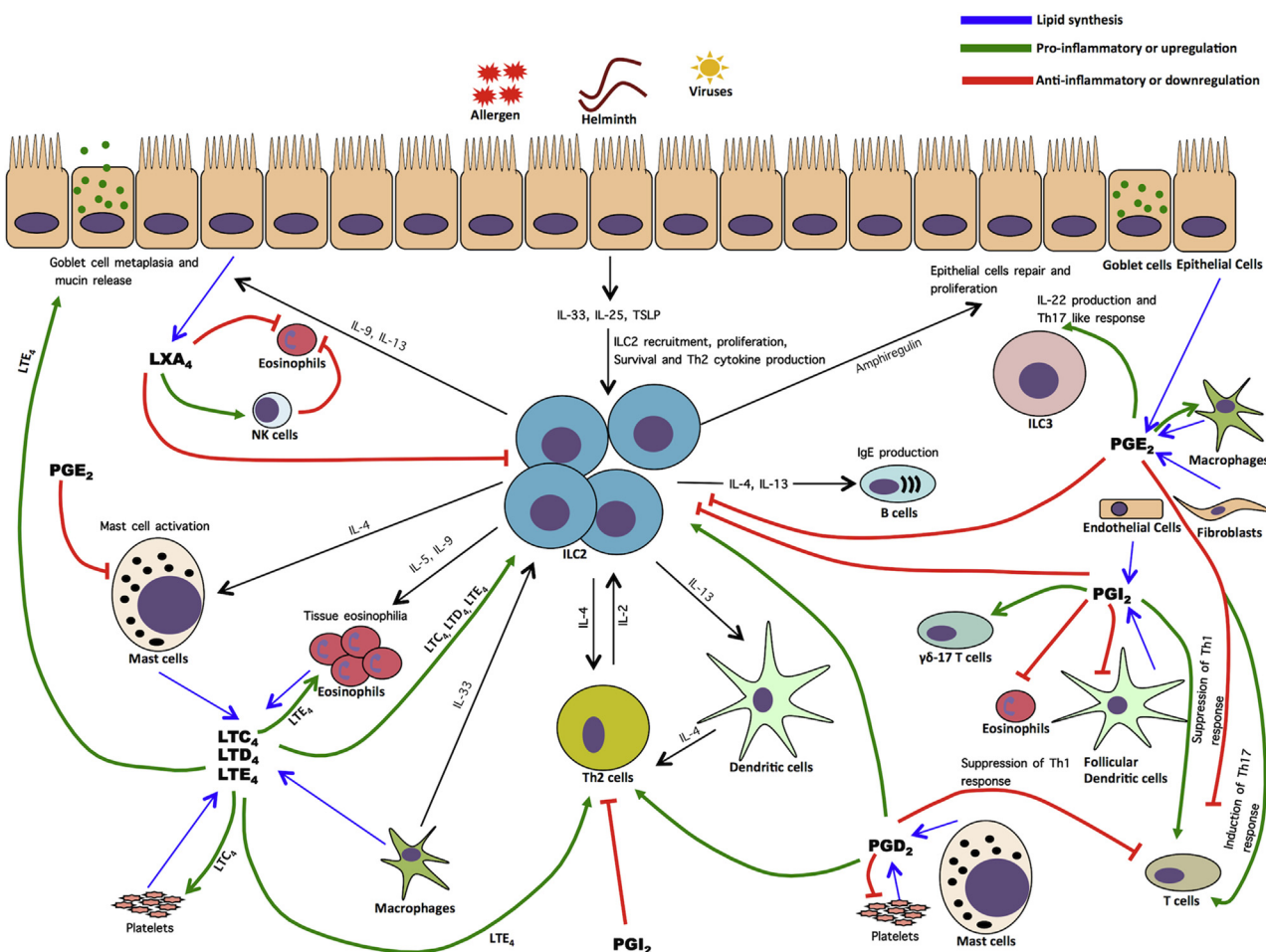


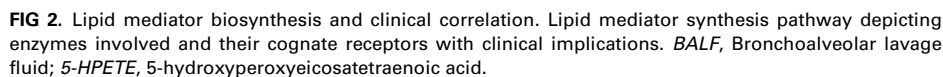
FIG 1. Production and effects of lipid mediators on type 2 inflammation. EpCs release IL-33, IL-25, and TSLP, which activate ILC2s and T_H2 cells and lead to T_H2 cytokine release. CysLTs, generated by mast cells, eosinophils, macrophages, and platelets, act on ILC2s and T_H2 cells. Mast cells and platelets are prime producers of PGD₂, which supports the type 2 response by activating ILC2s and T_H2 cells and suppresses the T_H1 response by inhibiting T-cell production of IFN- γ and IL-2. PGE₂, a product from EpCs, macrophages, and fibroblasts, suppresses activation of ILC2s but also enhances IL-33 synthesis by macrophages and potentiates a T_H17 -like effector response from group 3 innate lymphoid cells (ILC3) and T cells. PGE₂ also has anti-inflammatory effects because it can block mast cell activation. PGI₂ has mostly anti-inflammatory roles on ILC2s, T_H2 cells, eosinophils, and follicular DCs. LXA₄ can also modulate the type 2 immune response by suppressing PGD₂-derived activation of ILC2s and promoting eosinophil apoptosis by natural killer (NK) cells.

Additionally, a population of conventional human T_H2 cells identified exclusively in subjects with allergic disease display ILC2-like features (including the expression and function of receptors for TSLP, IL-33, and IL-25). These cells, termed pathogenic effector T_H2 cells or " T_H2A " cells have innate-like functions such that they no longer require specific antigen exposure for activation and type 2 cytokine production.^{9,10} They might account for the majority of cytokine-producing T cells in patients with allergic disease. Thus the mechanisms that control innate and adaptive lymphoid effectors, both positively and negatively, carry not only pathobiological significance but also potential therapeutic implications, especially in patients with severe disease.

Lipid mediators derived from arachidonic acid (AA) play substantial roles in the control of ILC2 and T_H2 cell function. AA is stored in membrane phospholipids and released at high levels

on cell activation. AA is metabolized to prostaglandins (PGs), leukotrienes (LTs), and other bioactive mediators through specific synthetic enzyme pathways.^{2,11} AA-derived bioactive lipids have receptor-specific inductive and suppressive effects that can influence the duration and magnitude of the immunopathology and end-organ dysfunction. This carries the potential for lipid mediator-targeted therapies to substantially affect allergic diseases.¹²⁻¹⁵

This review will cover our current understanding of the proinflammatory and anti-inflammatory functions of AA-derived lipids, their cells of origin, and their receptors. Although many cell types (including mast cells, basophils, and eosinophils) relevant to type 2 immunopathology express these receptors, we will focus primarily on the effects of lipid mediators on ILC2s and T_H2 cells, as well as their upstream cytokine sources, where applicable, because of the recent increase in published literature on this subject.



Biosynthesis

Receptors

Clinical correlation

Patients with spontaneous asthma exacerbations have high urinary LTE₄ levels relative to their baseline values. Both the 5-LO inhibitor zileuton and selective CysLT₁R antagonists provide

TABLE I. Lipid mediator receptors and their cellular expression: Outline of various cell types known to express lipid mediator receptors

Receptor(s)	Lipid mediator	Cell types	
		Mouse	Human
CysLT ₁ R = CysLT ₂ R	LTC ₄	ILC2s, DCs, platelets, mast cells, endothelial cells	EpCs, bronchial smooth muscle, mast cells, macrophages, cardiac Purkinje cells, endothelial cells
CysLT ₁ R >>> CysLT ₂ R	LTD ₄	ILC2s, T _H 2 cells, DCs, platelets, EpCs	ILC2s, T _H 2 cells, EpCs, bronchial smooth muscle, mast cells, macrophages
CysLT ₃ R	LTE ₄	Airway EpCs	Vascular smooth muscle cells
DP1	PGD ₂	Langerhans cells, DCs, mast cells	Microglia, astrocytes, endothelial cells, platelets, DCs, mast cells, eosinophils, basophils and T cells, alveolar macrophages
CRTH2/DP2		T _H 2 cells, eosinophils, basophils, T cells	Eosinophils, basophils, ILC2s, T _H 2 cells, peT _H 2 cells, mast cells, alveolar macrophages
EP ₁	PGE ₂	Macrophages	
EP ₂		DCs, T cells, mast cells, eosinophils, macrophages	Mast cells, eosinophils, neutrophils, T cells, DCs, ILC2s, fibroblasts
EP ₃		Mast cells, eosinophils, macrophages	Eosinophils
EP ₄		DCs, T cells, ILC3s, mast cells, eosinophils, macrophages	ILC3s, mast cells, eosinophils, T cells, DCs, cutaneous Langerhans cells, ILC2s, airway smooth muscle
IP	PGI ₂	DCs, ILC2s, CD4 ⁺ T cells, T _H 2 cells, eosinophils	DCs, ILC2s
ALX/FPR	LXs		ILC2s, NK cells

NK, Natural killer; peT_H2, pathogenic effector T_H2.

significant protection from asthma exacerbations in controlled trials, verifying the contribution of cysLTs to asthma exacerbations.^{13,14,26} Baseline levels of urinary LTE₄ are significantly increased in obese asthmatic patients than in nonobese asthmatic patients.²⁷ In preschool children increased urinary LTE₄ levels correlate with high serum IgE levels and strongly predict subsequent asthma development.²⁸ The early observations that inhaled LTE₄ induced eosinophil accumulation in the bronchial mucosa of patients with mild asthma were the first evidence that cysLTs promote type 2 immunity.²⁹ Administration of zileuton or montelukast (CysLT₁R inhibitor) reduce blood eosinophil counts.³⁰⁻³²

In patients with aspirin-exacerbated respiratory disease (AERD), cysLT overproduction is accompanied by severe asthma and chronic eosinophilic rhinosinusitis. The symptomatic improvement afforded these patients by cysLT-targeted drugs is consistent with the role of cysLTs as inducers and amplifiers of type 2 immunopathology in human subjects, especially those with AERD (Fig 2).^{31,33,34}

Activation of T_H cells and ILC2s

Human T_H2 cells, but not T_H1 cells, express CysLT₁R, and their stimulation with cysLTs elicited IL-13 production.^{4,35} Curiously, although the response is completely blocked by CysLT₁R antagonists, LTE₄ is more potent than LTD₄ for this effect. In addition, the effect of LTE₄ on human T_H2 cells is amplified by PGD₂, which acts synergistically with LTE₄ to induce not only T_H2 cytokines but also IL-22, IL-8, and GM-CSF.³⁶ Human ILC2s also express CysLT₁R, and this expression is greater in cells from atopic subjects compared with nonatopic control subjects. Isolated human ILC2s showed induced migration, survival, and type 2 cytokine production on *ex vivo* stimulation with LTE₄ to a greater extent than with LTD₄.³⁷ Furthermore, as is the case

for human T_H2 cells, LTE₄ and PGD₂ have synergistic effects with IL-25, IL-33, and TSLP on ILC2s *in vitro* to enhance type 2 cytokine production.

Mouse lung ILC2s proliferate and generate IL-4, IL-13, and IL-5 in response to exogenous LTC₄ and LTD₄, which can be blocked by CysLT₁R antagonists and is absent in mice lacking CysLT₁R.³⁸ LTC₄ and LTD₄ also synergize with IL-33 to promote T_H2 cytokine generation.^{39,40} Notably, although LTC₄, LTD₄, and LTE₄ can all expand and activate lung ILC2s in mice, the effects of LTE₄ appeared to be indirect and (unlike human ILC2s) independent of CysLT₁R.^{39,41} These studies support a role for cysLTs in amplifying inflammation in type 2 immunity by acting at both the innate and adaptive lymphocyte compartments.

Effects on EpCs

Human nasal EpCs express both CysLT₁R and CysLT₂R based on immunostaining of mucosal biopsy specimens.⁴² Although studies examining the role of cysLTs in EpC function are sparse, CysLT₁R signaling conferred protection from epithelial damage in a model of airway injury induced by (Cl₂)-elicited oxidative stress.⁴³ CysLT₃R/GPR99 is expressed dominantly by murine respiratory EpCs. Intranasal administration of LTE₄ to wild-type (WT) mice elicited mucin release by goblet cells, which was abrogated in CysLT₃R-null mice. Endogenous CysLTs-GPR99 signaling was also crucial for *Alternaria alternata*-induced mucin release.²³ Additionally, lung EpC-derived IL-33 is sharply increased in *Dermatophagoides farinae* extract (Df)-treated microsomal PGE₂ synthase (*Ptges*) null mice, which show strong cysLT-driven type 2 pathology relative to WT control mice. The increase in IL-33 levels was abrogated in LTC₄S-null mice, which was attributable to endogenous cysLT signaling through CysLT₂R.^{41,44} Given the ability of IL-33 to activate ILC2s synergistically with cysLTs

acting at CysLT₁R,³⁹ these findings imply cooperation between at least 2 cysLT receptors in regulating ILC2 homeostasis in inflammation.

PGs

Biosynthesis

Essentially all cell types generate COX products or PGs. Two COX enzymes, COX-1 and COX-2, cyclize AA to PGG₂ and then to PGH₂ through endoperoxidase activity. COX-1 accounts for constitutive PG generation in most cell types, whereas COX-2 expression can be induced or upregulated in response to signaling through exogenous (eg, endotoxin) and endogenous (eg, IL-1) danger signals. Such stimuli sharply increase PG production, which reflects COX-2 function. PGH₂ serves as a substrate for conversion to one of 5 different terminal PGs (PGD₂, PGE₂, PGF₂, PGI₂, and thromboxane [TX] A₂, respectively) by corresponding PG synthases. Mast cells express both hematopoietic prostaglandin D synthase (hPGDS) and TXA₂ synthase and can generate PGD₂ and smaller amounts of TXA₂.^{45,46} Platelets also express both hPGDS and TXA₂ synthase, although TXA₂ is their primary COX product.⁴⁷ EpCs, fibroblasts, and macrophages generate PGE₂ because of their expressions of microsomal prostaglandin E₂ synthase 1 (mPGES-1), the most dominant of 3 enzymes capable of catalyzing the formation of PGE₂.^{46,48,49} PGI₂ synthase is expressed prominently by endothelial cells and follicular dendritic cells (DCs), which generate PGI₂ (also known as prostacyclin) as their dominant COX pathway product. Finally, the human PGF synthase enzyme is expressed primarily in lungs, where it catalyzes 2 reactions: formation of PGF₂α from PGH₂ and conversion of PGD₂ to 9α, 11β-PGF, which is a potent bronchoconstrictor.^{50,51} All of the terminal PGs have short biological half-lives, suggesting that they function primarily in autocrine circuits, as well as paracrine cell-cell interactions over short distances (Fig 2).⁴⁷

PGD₂

Receptors. PGD₂ signals directly through 2 G protein-coupled receptors (GPCRs) termed D prostanoid (DP)₁ and DP₂, respectively, or chemoattractant receptor-homologous molecule expressed on T_H2 cells (CRTH2).⁵² DP₁ receptors are homologous to other PG-responsive GPCRs, signal through stimulatory G proteins, and are expressed by endothelial cells, platelets, DCs, mast cells, eosinophils, basophils, and T cells.⁵³ DP₂ receptors are more homologous to chemokine receptors, signal through inhibitory G proteins, and are strongly expressed by eosinophils, basophils, ILC2s, and human T_H2 cells (see below).⁵³ Combined with the fact that mast cells are the dominant sources of PGD₂, distribution of the DP receptors suggests its capacity to promote communication from mast cells to both the innate and adaptive immune systems. The PGD₂ metabolite 9α-11β-PGF₂ functions as a bronchoconstrictor through T prostanoid receptors and likely accounts for the decrease in airflow that results from inhalation of PGD₂ by human subjects.^{51,54} Another metabolite, 15-deoxy PGJ₂α, is an agonist for peroxisome proliferator-activated receptor γ.^{55,56} Thus some PGD₂ effects *in vivo* likely occur independently of its cognate GPCRs (Table I).

Clinical correlation. PGD₂ is released from airway mast cells in response to provocative challenges of susceptible hosts with allergens or (in the case of AERD) nonselective COX

inhibitors. Nasal polyps contain high levels of PGD₂, and numbers of hPGDS⁺ cells in nasal polyps correlate with asthma risk.^{57,58} Also, both PGD₂ levels and numbers of cells expressing CRTH2⁺ cells were higher in bronchoalveolar lavage (BAL) fluid from patients with severe asthma than those with milder disease.^{57,59} Similar findings were reported in the tissues from patients with EoE.^{60,61} Several CRTH2 antagonists (ARRY 502, BI-671800, QAW-039, and OC000459) have been tested in clinical trials and have shown encouraging results in patients with asthma⁶² and those with EoE,⁶³ further supporting the role of PGD₂ in type 2 immunopathology and its potential as a therapeutic target (Fig 2).

Effects on type 2 lymphocytes. CRTH2 expression is highly specific to T_H2 cells among CD4⁺ cells in human subjects and is also restricted to ILC2s among human innate lymphocyte subsets. PGD₂ elicits chemotaxis and generation of IL-5 and IL-13 by both T_H2 cells and ILC2s and sustains survival of T_H2 cells. Notably, T_H2/T_H2A cells express both hPGDS and COX-2 in addition to CRTH2 and generate PGD₂ when activated *ex vivo*, which is suggestive of an autocrine amplification loop.⁹ These studies suggest that endogenous PGD₂-CRTH2 signaling can regulate the survival and cytokine production of both innate and adaptive effector lymphocytes found in type 2 immunopathology. Additionally, DP₁ signaling has been shown to block IFN-γ and IL-2 expression in unfractionated human T cells.⁶⁴ Thus PGD₂ could potentiate type 2 immunity by suppressing T_H1 cytokine production, as well as direct CRTH2-mediated promotion of T_H2 cytokine generation. Because CRTH2 is also expressed by eosinophils and basophils,⁶⁵ direct chemotaxis of effector cells is another likely consequence of CRTH2 signaling.

PGE₂

Receptors. Of all PGs, PGE₂ is the most ubiquitous because of its production by multiple cell types and functional complexity caused by signaling through 4 separate GPCRs, termed E-prostanoid receptor (EP) 1 to 4.⁶⁶ These receptors are expressed broadly and in various combinations by both immune and nonimmune cells. Consequently, PGE₂ has well-defined proinflammatory and anti-inflammatory effects that depend on context.^{67,68} PGE₂ production *in vivo* increases sharply during inflammatory responses,⁶⁷ reflecting the sequential function of COX-2 and mPGES-1. Although PGE₂ can facilitate T_H17-type immunopathology through EP₂- and EP₄-mediated effects on DCs and T cells in animal models^{69,70} and can facilitate the function of group 3 innate lymphoid cells through EP₄ receptor,⁷¹ it is substantially bronchoprotective and anti-inflammatory in the setting of type 2 airway immunopathology in human subjects and has similar effects in both mouse and rat models (Table I).

Clinical correlation. When administered through inhalation to subjects with atopic asthma, PGE₂ attenuates both early- and late-phase responses to allergen and decreases the recruitment of both eosinophils and basophils to the lung during the late phase.⁷² In addition, PGE₂ inhalation significantly decreases levels of PGD₂ and cysLTs in BAL fluid of atopic asthmatic patients collected after allergen challenge.⁷³

These findings are consistent with the reported effects of PGE₂ in suppressing mast cell activation and inhibiting 5-LO activation through protein kinase A-dependent serine phosphorylation.⁷⁴⁻⁷⁶ Based on studies using precision-cut human lung slices, PGE₂ stabilizes airway mast cells and prevents 5-LO activation primarily

through EP₂ receptor signaling and also acts as a modest direct bronchodilator by acting at EP₄ receptors on airway smooth muscle.⁷⁷

The role of PGE₂ in regulating airway pathology is most evident in patients with AERD, in which both impaired production of PGE₂ and reduced EP₂ receptor expression, function, or both are reported.⁷⁸⁻⁸¹ Depletion of residual PGE₂ by aspirin and other drugs that inhibit COX-1 might account for the cysLT- and mast cell-dependent physiologic responses observed in patients with this disease.⁴⁶ Accordingly, inhalation of PGE₂ by patients with AERD before provocative challenge with aspirin prevents both the characteristic reduction in FEV₁ and the increase in urinary LTE₄ levels, which are indicative of 5-LO activation. These deficiencies might explain the high levels of eosinophilic inflammation, ongoing mast cell activation, and overproduction of cysLTs characteristic of the disease. This hypothetical role for PGE₂ in patients with AERD is strongly supported by animal models (Fig 2).⁸²

Effects on lymphocytes. PGE₂ exerts complex effects on T-cell functions that depend on context. PGE₂-EP₂ signaling in naive human T cells facilitates polarization to T_H17-type effector function, inducing the receptors for both IL-23 and IL-1.⁶⁹ Additionally, PGE₂ signaling through EP₄ receptors suppresses production of both IL-10 and IFN- γ . In murine T cells PGE₂ can facilitate both T_H17 and T_H1 effector function *in vitro* and is important for the development of T_H17-driven neuropathology in patients with experimental autoimmune encephalomyelitis. In contrast, PGE₂ potentially suppresses IL-5 generation by polyclonally activated human T cells and also suppresses IL-2, IL-4, and IL-5 generation by a human T-cell line while suppressing proliferation of these cells. The receptor or receptors responsible were not determined in this study, although cyclic AMP was implicated. The effects of PGE₂ on T-cell responses might be concentration specific, with suppressive effects observed at micromolar range concentrations and stimulatory effects at nanomolar concentrations.⁸³

To date, no studies have addressed whether PGE₂ differentially affects the function of T_H1, T_H2, or T_H17 effector cells and whether these effects are reflected in the bronchoprotective effects of PGE₂ *in vivo*. Recent studies suggest that PGE₂/EP₄ receptor signaling stimulates mouse group 3 innate lymphoid cells (which exhibit T_H17-like effector functions) to generate IL-22 and restrain systemic responses to bacteria.⁷¹ EP₂ receptor transcript is expressed strongly by human ILC2 cells,⁸⁴ and PGE₂ signals through both EP₂ and EP₄ receptors to suppress proliferation and T_H2 cytokine generation by this cell type.⁸⁵

Modulation of cytokine expression by macrophages.

Although PGE₂ suppresses type 2 inflammation in most settings, a recent study demonstrated that mice lacking mPGES-1 showed significantly reduced lung eosinophilia and ILC2 expansion compared with WT control mice in response to repetitive inhalation challenges with an extract from the allergenic mold *A alternata*. These reductions corresponded to diminished expression of IL-33 by lung cells in the mPGES-1-deleted mice. Bone marrow-derived macrophages from mice lacking mPGES-1 or EP₂ receptors displayed sharply diminished LPS-induced expression of IL-33 transcript and protein relative to WT control cells. This study highlights the complexity of the effects of PGE₂ in the lung and suggests that PGE₂ is anti-inflammatory in most settings in human and mouse studies but has proinflammatory effects toward IL-33 production in murine macrophages.⁴⁹

PROSTACYCLIN Receptors

PGI₂, also known as prostacyclin, is a short-lived COX product generated by endothelial cells and follicular DCs. It signals through the stimulatory G protein-linked I prostanoid (IP) receptor. Although best known as a vasodilator and potent inhibitor of platelet activation, PGI₂ also has prominent inhibitory functions in models of allergic pulmonary inflammation.⁸⁶⁻⁸⁸ Mice bearing targeted deletions of IP receptors and prostaglandin I synthase (PGIS), respectively, show sharply augmented inflammatory responses to antigen sensitization and challenge,^{89,90} whereas stable PGI₂ analogs show suppressive effects. As noted below, these effects reflect the actions of PGI₂ at several cellular control points (Table I).

Clinical correlation

PGI₂ is the most abundant COX product generated spontaneously by human lung fragments *ex vivo*,⁹¹ as reflected by detection of the stable metabolite 6-keto PGF1- α . These quantities increase substantially when lung fragments are sensitized passively with IgE and challenged with anti-IgE.⁹² PGI₂ generation also increases substantially in BAL fluid collected from atopic human subjects after segmental allergen inhalation challenge. Because mast cells do not generate PGI₂, it seems likely that these increases reflect the activation of endothelial cells. Inhalation of PGI₂ by subjects with mild asthma caused decreases in FEV₁, presumably reflecting vascular engorgement, but also blocked bronchoconstriction to subsequent administrations of methacholine or PGD₂.⁹³ Although it is presently unknown whether the suppressive effects of PGI₂ on type 2 inflammation are recapitulated in human subjects, IP receptor agonists (epoprostenol, treprostinil, and iloprost) are US Food and Drug Administration approved for the treatment of pulmonary arterial hypertension⁹⁴ and should permit such studies (Fig 2).

Suppression of lymphocyte activation

IP receptors are highly expressed on both CD4⁺ effector T cells and T_H2 cells. Adoptive transfer of transgenic ovalbumin (OVA)-specific mouse T_H2 cells that had been pretreated with PGI₂ showed a significant attenuation of pulmonary inflammation and AHR compared with transfer of PGI₂-untreated T_H2 cells. This effect was attributed to a loss of CCL17-induced CD4⁺ T_H2 cell chemotaxis. IP-null regulatory T cells display reduced suppressive function compared with WT cells, and IP-null effector T cells are less responsive to suppression by WT regulatory T cells than are WT effector T cells.⁹⁵ PGI₂-IP signaling also regulates IL-6 release from lung eosinophils and DCs to modulate intraepithelial $\gamma\delta$ -17 T cells. Mice lacking IP receptors demonstrate reduced $\gamma\delta$ -17 cells in the thymi of naive mice and also in the lungs in response to allergen challenge. Conversely, iloprost augmented IL-17 production by $\gamma\delta$ T cells in an IL-6-dependent manner and significantly reduced airway inflammation, suggesting a key immunoregulatory role of PGI₂ in the development of innate intraepithelial $\gamma\delta$ -17 cells.⁹⁶

PGI₂ can directly downregulate production of T_H2 cytokines from T_H2-polarized mouse splenic CD4⁺ cells on restimulation in the presence of PGI₂ analogs, with partial dependence on IP receptor.⁹⁷ Furthermore, PGI₂ has also been shown to increase

production of T_H2 -suppressive IL-10 from T_H2 -polarized $CD4^+$ cells.⁹⁸ Another *in vivo* study reported that PGI_2 reduces airway T_H2 -mediated inflammation by suppressing $CD4^+$ T_H2 cell recruitment to the lungs and demonstrated that mice sensitized and challenged with OVA and receiving T_H2 -polarized $CD4^+$ OVA-specific cells from D011.10 mice, along with IL-2 and PGI_2 , exhibit lower levels of T_H2 response.⁹⁹

More recent studies reveal a potential role for IP signaling in the function of ILC2s. Stimulation of mouse lung ILC2s with cicaprost inhibited their proliferation induced by IL-33¹⁰⁰ while facilitating their entry into apoptosis. In addition, cicaprost significantly inhibited IL-5 and IL-13 production from murine bone marrow-derived ILC2s stimulated with IL-33. Similar observations were also made with sorted human ILC2s in culture.¹⁰⁰ Moreover, in a murine model of repeated *Alternaria* species challenge, IP receptor-null mice showed significantly increased numbers of IL-5- and IL-13-producing ILC2s compared with WT controls.¹⁰⁰ This study suggests that endogenous PGI_2 can restrain the extent of ILC2 activation and resultant immunopathology during innate responses to proteases.

LIPOXINS

Biosynthesis and receptors

Lipoxin (LX) A_4 and LXB_4 are short-lived eicosanoids that arise from transcellular metabolism of AA through cooperative oxidation pathways. In the vasculature LTA_4 produced by activated leukocytes can be converted to LXs by platelet 12-LO. In the lung parenchyma LTA_4 can be converted to LXs by EpC 15-LO. LXs can also be formed by transformation of 15-LO-derived 15-hydroperoxy-eicosatetraenoic acid (15-H[p]ETE) by 5-LO. 15-Epimer-LXs are produced by 5-LO-mediated conversion of 15(R)-hydroxyeicosatetraenoic acid (15[R]-HETE) to 15-epi- LXA_4 and 15-epi- LXB_4 . Once synthesized, LXs exert anti-inflammatory effects at a number of cellular targets, at least some of which are mediated by ALX/FPR (lipoxin A_4 receptor or formyl peptide receptor), a GPCR (Fig 2 and Table I).

Clinical correlation

LXs are classified as proresolving mediators, and anomalies in their signaling or production have been associated with asthma severity. Blood levels of LXA_4 and leukocyte LXA_4 generation are reduced in subjects with severe asthma relative to those with milder disease.¹⁰¹ Stable LXA_4 analogs have shown promise in various models of inflammatory diseases, including asthma, although no human studies exist to date (Fig 2).

Effects on ILC2s

Human ILC2s and natural killer cells express ALX/FPR. A recent study demonstrated that LXA_4 suppressed PGD_2 -induced production of IL-13 by ILCs and also enhanced the proapoptotic effects of natural killer cells on autologous eosinophils. These studies extend the potential relevant cellular targets of LXA_4 to the lymphoid compartment and suggest a mechanism or mechanisms by which reduced production of LXA_4 can potentiate the severity of type 2 inflammation in asthmatic patients.¹⁰²

CONCLUSIONS

The recognition that eicosanoids regulate the function of lymphoid effectors of allergic disease has sparked renewed interest in lipid mediator biology. It is possible that at least some of the modest efficacy of existing drugs targeting 5-LO and $CysLT_1R$ in retrospect reflect the role of $cysLT$ s in control of ILC2s and the lymphoid compartment. Prominent synergistic effects of LTE_4 (mediated by $CysLT_1R$) and PGD_2 (mediated by $CRTH2$) on both T_H2 cells and ILC2s, along with suppressive effects of PGI_2 , PGE_2 , and LXA_4 identified in animal models of type 2 immunopathology, suggest additional opportunities for therapeutic targeting. Because all of these effects are mediated by GPCRs, which are readily targetable with antagonists, agonists, or both, it is possible that single drugs or combinations of such drugs could provide sufficient efficacy to serve as alternatives to therapies with potential toxicity (glucocorticoids) or prohibitive expense (biologics).

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