Aspirin sensitivity: Lessons in the regulation (and dysregulation) of mast cell function

Joshua A. Boyce, MD *Boston, Mass*

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Activity Objectives:

1. To recognize that aspirin-exacerbated respiratory disease (AERD) is not an immune-mediated drug allergy.
2. To understand the importance of an endogenous prostaglandin (PG) E2 as a check against mast cell activation and the evidence for deficiencies in COX-2–derived PGE2 and E prostanoid 2 receptor signaling in patients with AERD.
3. To recognize the evidence that mast cells are persistently activated at steady state in patients with AERD and that this activation is markedly increased with pharmacologic inhibition of COX-1.
4. To understand that steady-state mast cell activation persists (and can even increase) on high-dose aspirin despite clinical improvements.

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The idiosyncratic activation of mast cells (MCs) in response to administration of nonselective COX inhibitors is a cardinal feature of aspirin-exacerbated respiratory disease (AERD). Older studies using MC-stabilizing drugs support a critical role for MCs and their products in driving the severe eosinophilic inflammation and respiratory dysfunction that is typical of AERD. Because patients with AERD react to all nonselective COX inhibitors regardless of their chemical structure, the mechanism of MC activation is not caused by classical, antigen-induced cross-linking of IgE receptors. Recent studies in both human subjects and animal models have revealed a complex and multifactorial process culminating in dysregulation of MC function and an aberrant dependency on COX-1–derived prostaglandin E_2 to maintain a tenuous homeostasis. This article reviews the factors most likely to contribute to MC dysregulation in patients with AERD and the potential diagnostic and therapeutic implications. (J Allergy Clin Immunol 2019;144:875-81.)

Key words: *Aspirin, asthma, leukotrienes, mast cells, prostaglandins*

Mast cells (MCs) abound in all barrier tissues, including the respiratory mucosa. Although their physiologic functions in healthy human subjects are unknown, animal studies strongly support a key role in the initiation and amplification of innate immune responses to microbial pathogens.[1] The functions of MCs in type 1 hypersensitivity responses that underlie anaphylaxis, urticaria, and acute allergen-driven episodes of rhinitis and atopic asthma are well established. MC-derived

From the Division of Allergy and Clinical Immunology, Brigham and Women's Hospital.

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Corresponding author: Joshua A. Boyce, MD, Division of Allergy and Clinical Immunology, Brigham and Women's Hospital, Hale Building for Transformative Medicine, 60 Fenwood Rd, Boston, MA 02115. E-mail: jboyce@rics.bwh.harvard.edu.

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Abbreviations used

AERD:	Aspirin-exacerbated respiratory disease
cysLT:	Cysteinyl leukotriene
$CysLT_1R$:	Type 1 cysteinyl leukotriene receptor
$CysLT_2R$:	Type 2 cysteinyl leukotriene receptor
EP_2:	E prostanoid 2
5-LO:	5-Lipoxygenase
LT:	Leukotriene
MC:	Mast cell
mPGES-1:	Microsomal prostaglandin E_2 synthase 1
PG:	Prostaglandin
PGD-M:	Stable urinary prostaglandin D_2 metabolite
ST2:	Suppressor of tumorigenicity 2 (IL-33 receptor)
TSLP:	Thymic stromal lymphopoietin

products, such as histamine, cysteinyl leukotrienes (cysLTs), prostaglandin (PG) D_2, cytokines, and chemokines, have functions in allergic diseases that are validated or strongly supported by experimental evidence.[2] The ability of blocking antibodies against the Fc portion of IgE to block allergen-induced early- and late-phase responses in the airways of atopic asthmatic patients[3] further validates the importance of this classical activation pathway in allergic disease.

Aspirin-exacerbated respiratory disease (AERD) is a distinctive syndrome, typically of adult onset, that is characterized by severe eosinophilic sinonasal disease with recurrent nasal polyposis, asthma (which is often but not uniformly severe), and pathognomonic clinical reactions to the ingestion of aspirin or any other drug that inhibits the enzymatic function of COX-1.[4] It affects approximately 7% of all asthmatic patients in the United States and as many as 14% of patients with severe asthma.[5] The pathophysiology of AERD involves dysregulated MC function, and MC-derived products contribute substantially to the baseline immunopathology of the disease.[6] Moreover, the pathognomonic clinical reactions to COX-1 active drugs are associated with marked activation of MCs through mechanisms that are poorly understood but are not due to IgE-dependent immune recognition of the drug.[7-9] This review summarizes the potential significance of MCs in patients with AERD and the recent studies that highlight potential mechanisms responsible for their dysregulation and activation in this context.

EVIDENCE TO SUPPORT A KEY ROLE FOR MCs IN PATIENTS WITH AERD

When activated, MCs generate leukotriene (LT) C_4, the parent of the cysLTs, through the 5-lipoxygenase (5-LO)/LTC_4 synthase pathway.[10] This pathway is shared with eosinophils, basophils, and monocytes. MCs also metabolize arachidonic acid through the COX pathway to generate especially large quantities of PGD_2.[11]

CysLTs and PGD_2 synergize to activate human innate group 2 lymphoid cells and T_H2 cells. CysLTs are the most potent known constrictors of the human airways,[12] elicit mucous secretion,[13] and activate IL-25–expressing airway brush cells.[14] Levels of the terminal cysLT metabolite LTE_4 can be measured in urine, as can stable metabolites (stable urinary prostaglandin D_2 metabolite [PGD-M]) of PGD_2, as time-weighted reflections of LTC_4 and PGD_2 generation, respectively. In patients with AERD, urinary levels of both LTE_4 and PGD-M exceed those in aspirin-tolerant control subjects by several fold,[15,16] which is consistent with ongoing MC activation. Administration of aspirin induces sharp additional increases in both mediators accompanied by increases in plasma levels of histamine (which might also reflect concomitant basophil activation) and (in some subjects) serum tryptase, confirming MC activation.

MC numbers are increased in the bronchial biopsy specimens and sinonasal mucosa of patients with AERD compared with aspirin-tolerant control subjects.[17,18] Thus AERD involves relative MC hyperplasia, persistent steady-state MC activation ("leaky MCs"), and marked unbraking of MC activation with COX-1 blockade. Importantly, the unbraking phenomenon occurs with all drugs (regardless of structure) that interfere with COX-1, indicating that reactions are not manifestations of IgE-dependent "drug allergy" but rather reflect an idiosyncratic dependency on 1 or more COX-1 products to maintain a tenuous homeostasis over MCs and other effector cells.

Several older studies using classical MC-stabilizing cromone drugs strongly suggest that both the steady-state MC "leak" and the incremental activation with COX-1 inhibition contribute substantially to AERD pathophysiology. Although administration of cromolyn has no acute effect on baseline lung function measurements in aspirin-tolerant asthmatic control subjects, it increased FEV_1 in patients with AERD within minutes of administration.[19] In another study, treatment with cromolyn for 1 week significantly decreased numbers of sputum eosinophils and sputum levels of eosinophilic cationic protein in patients with AERD.[20] Administration of cromolyn or nedocromil to patients with AERD blocks the reduction in FEV_1 that occurs with aspirin challenge,[21] as well as the accompanying increase in urinary LTE_4 levels.[22] Collectively, these studies strongly support the importance of MCs and their mediators in both steady-state respiratory dysfunction and clinical reactions to COX-1 inhibition in patients with AERD, emphasizing the importance of understanding the idiosyncratic mechanisms responsible for the dysregulated function of MCs in patients with this disease.

FACTORS CONTRIBUTING TO MC ACTIVATION IN PATIENTS WITH AERD

Dysregulation of the PGE_2/E prostanoid 2 receptor system

PGE_2 is a ubiquitous COX product with MC-stabilizing properties. It is generated constitutively at steady state and inducibly at very high levels during inflammatory responses. Epithelial cells, fibroblasts, and macrophages all generate substantial quantities of PGE_2 when stimulated *ex vivo* with IL-1β or LPS. This response reflects inducible expression of COX-2 and microsomal prostaglandin E_2 synthase 1 (mPGES-1), the principal terminal synthase responsible for generating PGE_2 during inflammatory responses, in concert with COX-2 (Fig 1, *A*). Compared with constitutively expressed COX-1, COX-2 is much less sensitive to inhibition by aspirin.[23] Consequently, PGE_2 derived from COX-2/mPGES-1 during inflammatory responses might be maintained even in the face of low-dose aspirin. PGE_2 signaling through the E prostanoid 2 (EP_2) receptor blocks MC degranulation in response to IgE receptor cross-linking[24] and dampens LT production by inducing protein kinase A–dependent phosphorylation of 5-LO.[25] Additionally, PGE_2 can elicit relaxation of airway smooth muscle

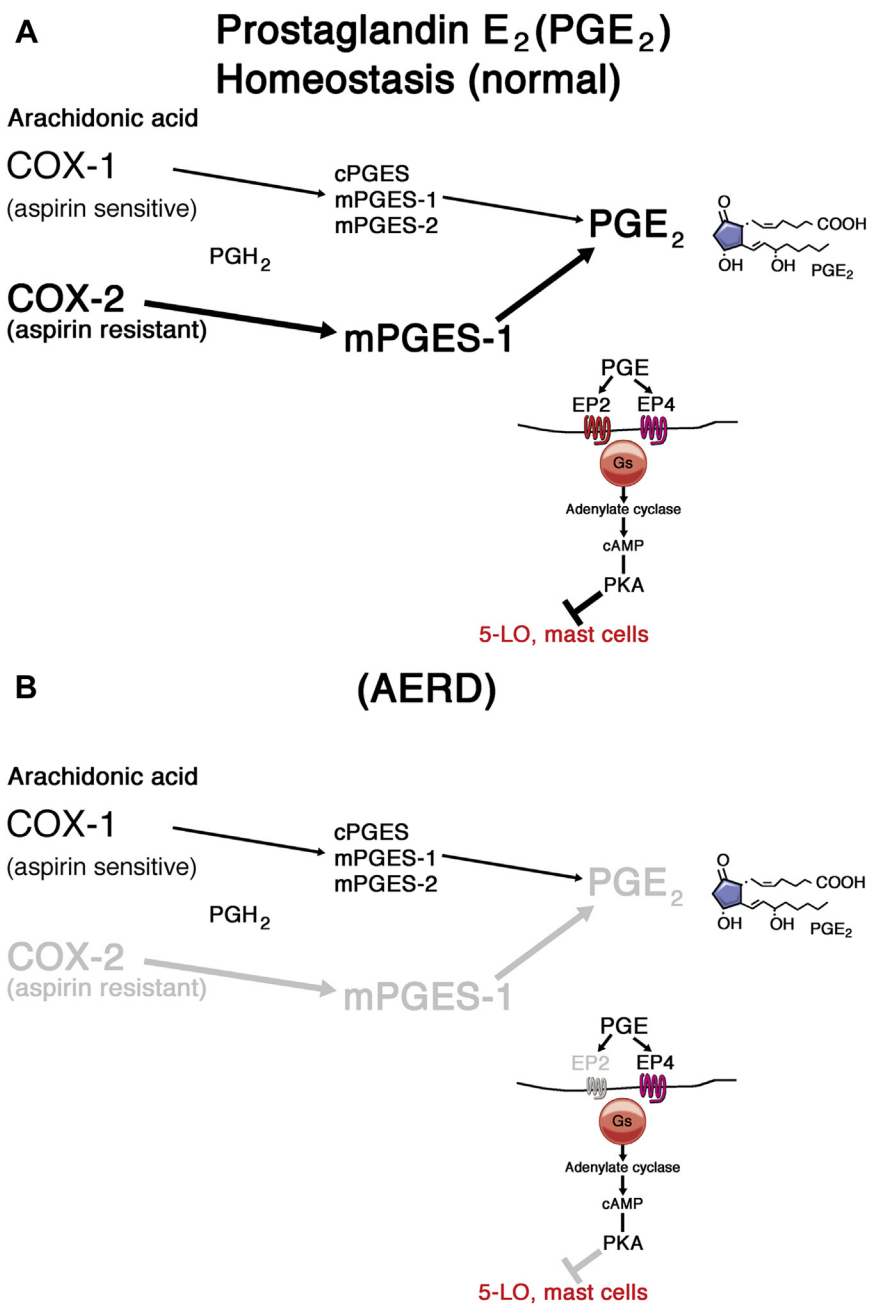

FIG 1. Biosynthesis of PGE_2 and its potential dysregulation in patients with AERD. **A,** Under physiologic conditions, PGE_2 derives from either constitutively expressed COX-1 or inducibly expressed COX-2. COX-derived PGH_2 can be converted to PGE_2 by 3 different terminal PGE_2 synthase *(PGES)* enzymes: cytosolic PGES *(cPGES)*, mPGES-1, and mPGES-2. During inflammation, the concomitantly induced expressions of COX-2 and mPGES-1 markedly increase PGE_2 production. Because COX-2 is much less sensitive to aspirin than COX-1, this increase is relatively resistant to low-dose aspirin. PGE_2 elicits signaling through EP receptors 1-4. EP_2 and EP_4 activate the cyclic AMP *(cAMP)*/protein kinase A *(PKA)* pathway that stabilizes MCs and blocks LT formation by phosphorylating 5-LO. **B,** In patients with AERD, impaired expression and function of the COX-2/mPGES-1 system renders PGE_2 production disproportionately dependent on COX-1 and susceptible to inhibition by low-dose aspirin. The effects of PGE_2 depletion are potentiated by diminished EP_2 receptor expression, leading to unbraking of MCs and 5-LO.

through EP_4 receptors. Thus PGE_2 can function to restrain MC activation and cysLT generation during inflammatory responses, and may also promote maintenance of airway caliber.

Impaired function of the COX-2/mPGES-1 system is associated with nasal polyposis, and can potentiate the risk of AERD (Fig 1). Nasal polyp levels of PGE_2 are markedly lower than in nonpolypoid sinonasal tissue,[26] and fibroblasts from nasal polyps show weak induction of COX-2 and mPGES-1 expression compared with cells from control subjects without polyps.[27] These levels tend to be lowest in samples from patients with

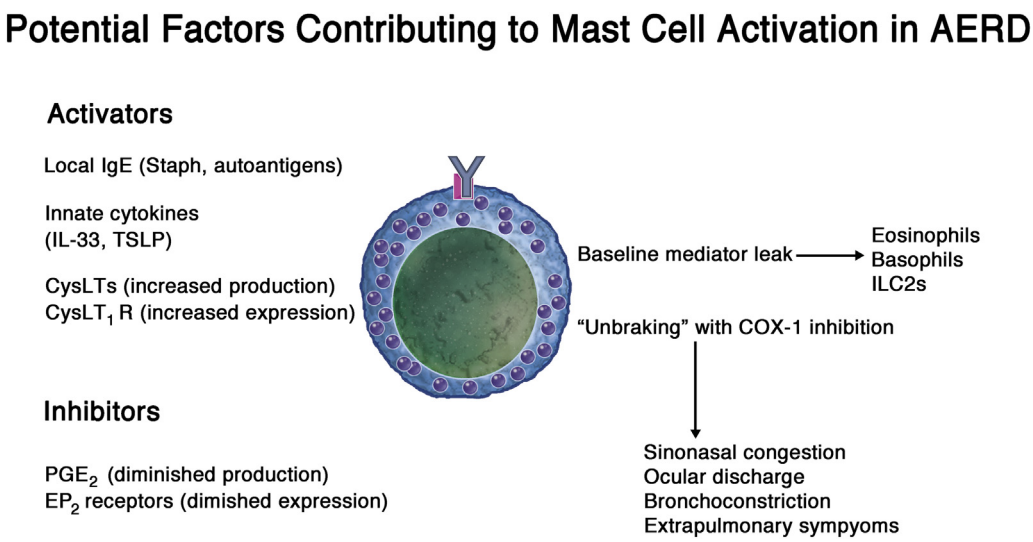

FIG 2. Hypothetical factors contributing to dysregulation of MC activation in patients with AERD. Occupancy of FcεRI, increased signaling through $CysLT_1R$, and locally derived innate cytokines (TSLP and IL-33) might conspire to promote an ongoing "leak" of PGD_2 and other MC products that facilitate eosinophilic pathology and baseline respiratory tissue dysfunction in patients with AERD. PGE_2-dependent maintenance of homeostasis is compromised by poor COX-2/mPGES-1 and EP_2 receptor function. Aspirin and other COX-1 inhibitors remove the brake provided by residual PGE_2, markedly destabilizing the system to permit marked MC activation and associated end-organ responses during pathognomonic reactions.

AERD.[28] Impaired expression of COX-2, mPGES-1, or both could render the maintenance of local PGE_2 generation disproportionately dependent on COX-1, predisposing to depletion of PGE_2 to less than a critical threshold when aspirin is administered (Fig 1, *B*). Indeed, clinical reactions generally occur at low threshold doses (80-160 mg) of aspirin that are typically selective for COX-1. Administration of a single dose of PGE_2 by means of inhalation blocks aspirin-induced changes in lung function and increases in urinary LTE_4 levels in patients with AERD,[29] which is consistent with a major role for endogenous PGE_2 as the critical COX-1–derived brake. The effect of depleting PGE_2 with COX-1 inhibition might be potentiated by reduced levels of EP_2 receptor expression by MCs (and other 5-LO–expressing leukocytes) in patients with AERD, as suggested by immunohistochemical staining of sinonasal and lung tissues (Fig 1, *B*).[30,31] Mice lacking either mPGES-1 or EP_2 receptors (*Ptges*$^{-/-}$ and *Ptger2*$^{-/-}$ mice, respectively) display AERD-like features, including aspirin-induced MC activation and increases in cysLT levels, supporting the likely importance of perturbations in these systems as disease-causing lesions.[32] Some studies support an epigenetic basis for these perturbations,[33,34] which is consistent with the acquired nature and persistence of AERD.

Although low-dose aspirin–induced depletion of COX-1–derived PGE_2 likely permits the triggering of MC activation during provocative challenges, high-dose aspirin (325-650 mg twice daily, a dose sufficient to block COX-2) after desensitization can paradoxically improve sinonasal function and reduce the frequency of recurrent polyps in patients with AERD.[35] Cahill et al[36] demonstrated that patients with AERD receiving high-dose aspirin have significantly increased total serum tryptase levels, as well as increased urinary levels of LTE_4 compared with their prechallenge baselines, suggesting paradoxical amplification of MC "leak," even in the face of substantial clinical improvement on aspirin. This increase in MC activation markers was paralleled by sharply reduced levels of PGE_2 metabolites in the urine, which is again consistent with the dependence of MCs on PGE_2 to maintain a tenuous homeostasis in patients with AERD. Because the tryptase was not fractionated in this study, it is not currently possible to ascertain whether ongoing MC degranulation is increased or whether depletion of PGE_2 dysregulates transcriptional control of tryptase synthesis. Notably, although PGD_2 production increases during reactions, the desensitized state on high-dose aspirin is accompanied by sharp reductions in urinary PGD-M levels.[7] Nasal polyp MCs express markedly greater levels of mRNA encoding COX-2 than COX-1,[16] potentially explaining why PGD_2 production resists inhibition during provocative challenges until the aspirin dose is escalated. Suppression of PGD_2 production (with its attendant activating and chemotactic effects for eosinophils, basophils, group 2 innate lymphoid cells, and T_H2 cells) could contribute to the therapeutic benefit of aspirin.[7]

Dysregulation of cysLT synthesis and cysLT receptor function

CysLTs contribute substantially to the baseline pathophysiology of AERD[37] and are essential to the pathognomonic reactions to aspirin.[38] Dysregulated synthesis of cysLTs in patients with AERD[15] is paralleled by strongly upregulated expression of the type 1 cysteinyl leukotriene receptor ($CysLT_1R$) on hematopoietic cells, including MCs, in the airways,[39] suggesting a mechanism favoring a state of end-organ hyperreactivity to endogenous cysLTs. Indeed, patients with AERD have a markedly greater sensitivity to bronchoconstriction induced by inhaled LTE_4 than do aspirin-tolerant asthmatic control subjects.[40] Both hyperreactivity to LTE_4 and overexpression of $CysLT_1R$ are reduced toward levels seen in aspirin-tolerant control subjects after treatment with high-dose aspirin.[39,40]

A study by Fischer et al[41] strongly suggested that endogenous cysLTs are required for the idiosyncratic MC activation

mechanism that characterizes AERD. In this study, the administration of the 5-LO inhibitor zileuton not only blocked incremental sinonasal symptoms in response to the challenge but also prevented the increase in nasal lavage fluid levels of tryptase.[41] Although endogenous cysLTs are not required for IgE-dependent degranulation of MCs in *ex vivo* systems,[42] exogenous cysLTs are sufficient to elicit calcium flux, cytokine production, and PGD_2 generation from human cord blood MCs.[42,43] Moreover, a recent study demonstrated that inhalation of LTE_4 by asthmatic patients (almost all of whom were aspirin-tolerant) induced markedly increased urinary levels of PGD_2, which are indicative of MC activation *in vivo*. This response was blocked by the $CysLT_1R$ antagonist montelukast.[44] Although cysLTs are very likely to signal directly to MCs to induce their activation, animal models suggest additional effects related to cysLT-dependent control of MC-active cytokines (see below).

Role of IgE and FcεRI

Although rates of atopy in patients with AERD vary depending on the study,[45,46] the disease frequently occurs in patients who lack IgE with specificity to inhalant allergens (some of whom nonetheless have total IgE levels greater than the normal range).[47] A study by Hayashi et al[48] demonstrated that treatment of patients with AERD with recombinant humanized anti-IgE (omalizumab) in an open-label protocol markedly improved symptomatic control of both asthma and sinonasal disease while decreasing urinary levels of LTE_4 and PGD-M by greater than 75% each. In a small placebo-controlled trial, Lang et al[49] demonstrated that omalizumab treatment for 16 weeks prevented clinical symptoms and increases in urinary LTE_4 levels in 5 of 7 subjects challenged with aspirin, whereas all 4 placebo-treated subjects experienced reactions. Thus despite the lack of evidence implicating classical allergen-induced MC activation in AERD physiology, these studies suggest that ongoing signaling through MC-associated IgE receptors permit and amplify activation responses to depletion of PGE_2. The nature of the antigens driving the IgE production remains to be determined, although local production of antibodies against staphylococcal antigens[50] and autoantigens[51] have been reported in nasal polyps. It is unknown whether levels of these antibodies distinguish patients with AERD from aspirin-tolerant control subjects.

Role of innate cytokines

MCs express receptors for both IL-33 and thymic stromal lymphopoietin (TSLP). Both cytokines are abundant in nasal polyps,[52] with mRNA for each localizing principally to epithelial basal cells.[53] IL-33 potently induces production of type 2 cytokines and chemokines by MCs *ex vivo*[54] and strongly induces COX-2–dependent production of PGD_2.[16,55] TSLP strongly potentiates these IL-33–induced effects,[16,54] suggesting that these resident tissue-derived cytokines can synergize to influence MC function *in vivo*. In patients with AERD, levels of TSLP expression in sinonasal tissue correlate strongly with urinary levels of PGD-M (and with MC-specific transcripts, such as tryptase, carboxypeptidase A3, and hematopoietic PGD_2 synthase), suggesting that TSLP conditions MCs for augmented function in this disease.[16] One study reported that the quantities of IL-33 protein in nasal polyp extracts from patients with AERD substantially exceeded those in non-AERD control samples.[56]

IL-33 might be especially important in regulating MC function in patients with AERD. In AERD-like *Ptges*$^{-/-}$ mice, antibody-mediated blockade of IL-33 or blockade of suppressor of tumorigenicity 2 (ST2; the IL-33 receptor) with a soluble Fc fusion protein completely prevents MC activation (with attendant release of proteases and production of cysLTs and PGD_2), as well as increases in airway resistance occurring in response to aspirin challenge.[56] These mice display high levels of lung IL-33 protein after induction of airway inflammation by house dust mite allergen. This induced expression of IL-33 in *Ptges*$^{-/-}$ mice requires endogenous cysLTs and signaling through the type 2 cysteinyl leukotriene receptor ($CysLT_2R$).[57] Moreover, cysLTs not only drive IL-33 expression by alveolar type 2 cells but also induce recruitment and activation of IL-33$^+$ platelets, the latter of which are necessary for the MC response to aspirin challenge. Mouse platelets release substantial amounts of preformed cytosolic IL-33 in response to *ex vivo* stimulation by LTC_4.[58] Notably, large numbers of extravasated platelets are present in nasal polyps from patients with AERD compared with those from aspirin-tolerant control subjects,[59] and stimulation of freshly excised human nasal polyp tissue with LTC_4 *ex vivo* results in release of substantial amounts of IL-33.[58] It is tempting to speculate that the high levels of IL-33 protein found in polyps from patients with AERD might partially reflect a cysLT-driven platelet store.

Notably, although IL-33 alone is insufficient to elicit degranulation of MCs *ex vivo*, it does cause degranulation of mouse MCs that are passively sensitized with IgE and can cause anaphylaxis in mice when IgE is present.[60] This finding suggests a potential interaction between IL-33/ST2 and IgE-driven pathways that are permissive for the leaky MC phenotype in patients with AERD and might help explain both the incremental degranulation of MCs with aspirin challenge and therapeutic responses to omalizumab.

PATHOPHYSIOLOGIC AND THERAPEUTIC IMPLICATIONS

MC activation in patients with AERD appears to be driven by complementary dysregulation of systems that respectively induce stabilization (PGE_2/EP_2) or activation (IgE, IL-33, and cysLTs) of MCs (Fig 2). Blockade of 5-LO with zileuton provides incremental improvement in sinonasal function for patients already treated with glucocorticoids.[37] It seems possible that the marked effect of zileuton on signs, symptoms, and biomarkers of reactions to aspirin might reflect inhibition of both direct ($CysLT_1R$-mediated)[44] and indirect ($CysLT_2R$-driven and IL-33–mediated) cysLT-dependent pathways that facilitate MC activation. Since high dose aspirin therapy increases the baseline rate of cysLT synthesis, the clinical benefit of this modality may relate to downregulation of CysLT1R expression (and resultant reduction in end-organ reactivity to LTE_4) by MCs and other relevant cell types.

The potential efficacy of dual-specific antagonists of $CysLT_1R$ and $CysLT_2R$ could exceed that of the existing $CysLT_1R$-selective drugs. Stable PGE_2 analogues that selectively stimulate the EP_2 receptor could inhibit MC activation (and other EP_2 receptor–bearing effector cells) and limit cysLT production without the cough-inducing effects that preclude the use of PGE_2 itself, although reduced expression of EP_2 might limit its efficacy in some subjects. The encouraging results of omalizumab in small trials[48,49] suggest a need for larger studies and compel further study of the antigens potentially responsible for driving local IgE

synthesis. The high levels of PGD_2 production in patients with AERD suggests that antagonists of the type 2 receptor for PGD_2 (also known as CRTH2) might have efficacy by suppressing tissue eosinophilia. Biologics under development that target IL-33 and ST2 should provide opportunities to validate potential causative pathways implicated in experimental models, as well as potential efficacy.

Lastly, the MC-depleting tyrosine kinase inhibitor imatinib was recently shown to improve lung function and airway reactivity in a population of patients with refractory asthma not selected for the presence or absence of AERD.[61] Although imatinib has other potential targets (eg, platelet-derived growth factor receptors) that might account for its benefits independent of MCs, it is possible that it could offer efficacy in patients with AERD given the strong MC activation signatures associated with the disease.

CONCLUSIONS

- Diminished levels of COX-2 and mPGES-1 expression likely impair PGE_2 generation in patients with AERD and render residual PGE_2 production highly dependent on COX-1.
- Reduced levels of EP_2 receptor expression on MCs and other effector cells can exacerbate the effects of depleting PGE_2 with aspirin and other COX-1 active drugs.
- The high levels of cysLT production in patients with AERD are accompanied by increased levels of $CysLT_1R$ expression on hematopoietic cells.
- Desensitization to aspirin downregulates $CysLT_1R$ expression and decreases end-organ reactivity to cysLTs, which might help explain clinical improvement despite substantial further increases in cysLT generation.
- Local IgE produced against *Staphylococcus* species or autoantigens in nasal polyps could synergize with IL-33 to promote ongoing MC activation, which is likely exaggerated in patients with AERD because of reduced PGE_2/EP_2 signaling and enhanced cysLT generation.

What we do know?

- **MCs contribute substantially to both steady-state respiratory dysfunction and pathognomonic reactions to aspirin and other COX-1-active drugs in patients with AERD.**
- **PGE_2 maintains an essential brake on MC activation.**
- **Local IgE and endogenous cysLTs contribute to the idiosyncratic activation mechanism in patients with AERD.**

What is still unknown?

- **The role of innate type 2 cytokines (IL-33 and TSLP) in conditioning MCs for activation in AERD**
- **The molecular basis of the impaired function of the endogenous PGE_2/EP_2 receptor system**

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