

Aspirin-exacerbated respiratory disease: Mediators and mechanisms of a clinical disease



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Key words: *Aspirin-exacerbated respiratory disease, cysteinyl leukotrienes, prostaglandin D₂, innate immune mechanisms, future targets*

Aspirin-exacerbated respiratory disease (AERD) is characterized by adult-onset asthma and severe chronic eosinophilic rhinosinusitis with nasal polyposis. AERD is not consistently associated with atopy, although serum total IgE levels can be increased. Steady-state levels of urinary or nasal lavage fluid mast cell activation products (histamine and tryptase) and leukotriene (LT) E₄, the stable metabolite of the cysteinyl leukotrienes (cysLTs), exceed those found in patients with aspirin-tolerant asthma and sinonasal disease.

Administration of aspirin or other drugs that inhibit COX-1 causes sharp additional increases in mast cell products, as well as marked incremental increases in LTE₄ levels, with accompanying decreases in lung function and increases in sinonasal dysfunction (Fig 1, A and B). The bronchoconstriction during reactions can be attenuated by the administration of cromolyn or nedocromil, implying a role for mast cells.¹ Although COX-1 inhibitors likely cause reactions by depleting homeostatic prostaglandin (PG) E₂, which stabilizes mast cells through PGE₂ receptor 2, the permissive factors responsible for ongoing mast cell activation and cysLT production remain poorly understood. Identifying causative mechanisms could lead to targeted and effective therapy for AERD.

CysLTs

CysLTs form from arachidonic acid metabolized by 5-lipoxygenase and leukotriene C₄ synthase (LTC₄S). LTC₄ is quickly converted in the tissue to LTD₄ (the most potent bronchoconstrictor) and then LTE₄. The clinical benefit of the 5-lipoxygenase inhibitor zileuton on basal respiratory symptoms, as well as its ability to shift the dose of aspirin needed to elicit symptoms, underscore the contribution of cysLTs to the respiratory symptoms classic of AERD.¹ Although mast cells likely

contribute substantially to the increase in cysLT levels provoked by reactions, the administration of zileuton curiously prevents the increases in nasal lavage tryptase levels that occur with reactions in patients with AERD.

Thus cysLTs from additional sources might be essential for triggering steps that are proximal to mast cell activation. These sources likely include tissue eosinophils, which strongly over-express LTC₄S in patients with AERD.² Platelets also express LTC₄S and can convert neutrophil-derived LTA₄ to LTC₄ by a shuttling mechanism when they adhere to granulocytes.³ Peripheral blood and the nasal polyp tissue of patients with AERD contain increased numbers of platelet-leukocyte aggregates when compared with those in aspirin-tolerant control subjects. These numbers directly correlate with urinary LTE₄ levels. Depletion of platelets and platelet-leukocyte aggregates from mice protects them from aspirin-induced increases in airway resistance and excessive cysLT generation in a model of AERD.⁴ Thus platelets might play an especially critical role in patients with AERD.

CysLTs signal through cysteinyl leukotriene 1 receptor (CysLT₁R) and cysteinyl leukotriene 2 receptor (CysLT₂R), which bind LTC₄ and LTD₄, and the recently described CysLT₃R, also known as GPR99, which binds LTE₄.¹ The CysLT₁R antagonists montelukast and zafirlukast improve nasal congestion and improve the safety of aspirin desensitization protocols by decreasing the severity of lower respiratory tract symptoms. Occasionally, they suppress symptoms sufficiently to lead to false-negative aspirin challenge results. The lack of antagonists for CysLT₂R has precluded an analysis of this receptor's function in patients with AERD, although mouse studies indicate that CysLT₂R can drive platelet-dependent eosinophil recruitment to the lung. Curiously, patients with AERD exhibit selectively increased airway reactivity to LTE₄, which is a weak and trivial agonist for CysLT₁R and CysLT₂R but has high affinity for GPR99.⁵ Bankova et al⁶ recently reported that GPR99 is essential for mucus secretion in both the upper and lower respiratory tract. It is presently unknown whether LTE₄-mediated changes in airflow in patients with AERD are mediated by GPR99 because the distribution of this receptor in human airways remains to be defined.

PGD₂

Mast cells generate abundant quantities of PGD₂, a product of arachidonic acid metabolized by COX and a hematopoietic PGD₂ synthase. PGD₂ elicits vasodilation, chemotaxis of eosinophils, basophils, innate lymphoid type 2 cells, and bronchospasm through signaling through the D-prostanoid type 1 receptor, the D-prostanoid type 2 receptor (CRTH2), and the T prostanoid receptor, respectively. Baseline levels of PGD₂ metabolites in the urine of patients with AERD exceed those seen in aspirin-tolerant asthmatic control subjects and increase more than 4-fold during aspirin-induced reactions. This increase in PGD₂ levels correlates with sinonasal symptoms, decrease in FEV₁,

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Supported by the National Institutes of Health (AI118804, AI078908, AI095219, AT002782, AI082369, HL111113, and HL117945) and by generous contributions from the Vinik Family.

Disclosure of potential conflict of interest: K.N. Cahill has received a grant from the National Institutes of Health. J.A. Boyce declares that he has no relevant conflicts of interest.

Received for publication May 25, 2016; revised August 19, 2016; accepted for publication September 7, 2016.

Available online October 19, 2016.

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J Allergy Clin Immunol 2017;139:764-6.

0091-6749/\$36.00

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<http://dx.doi.org/10.1016/j.jaci.2016.09.025>

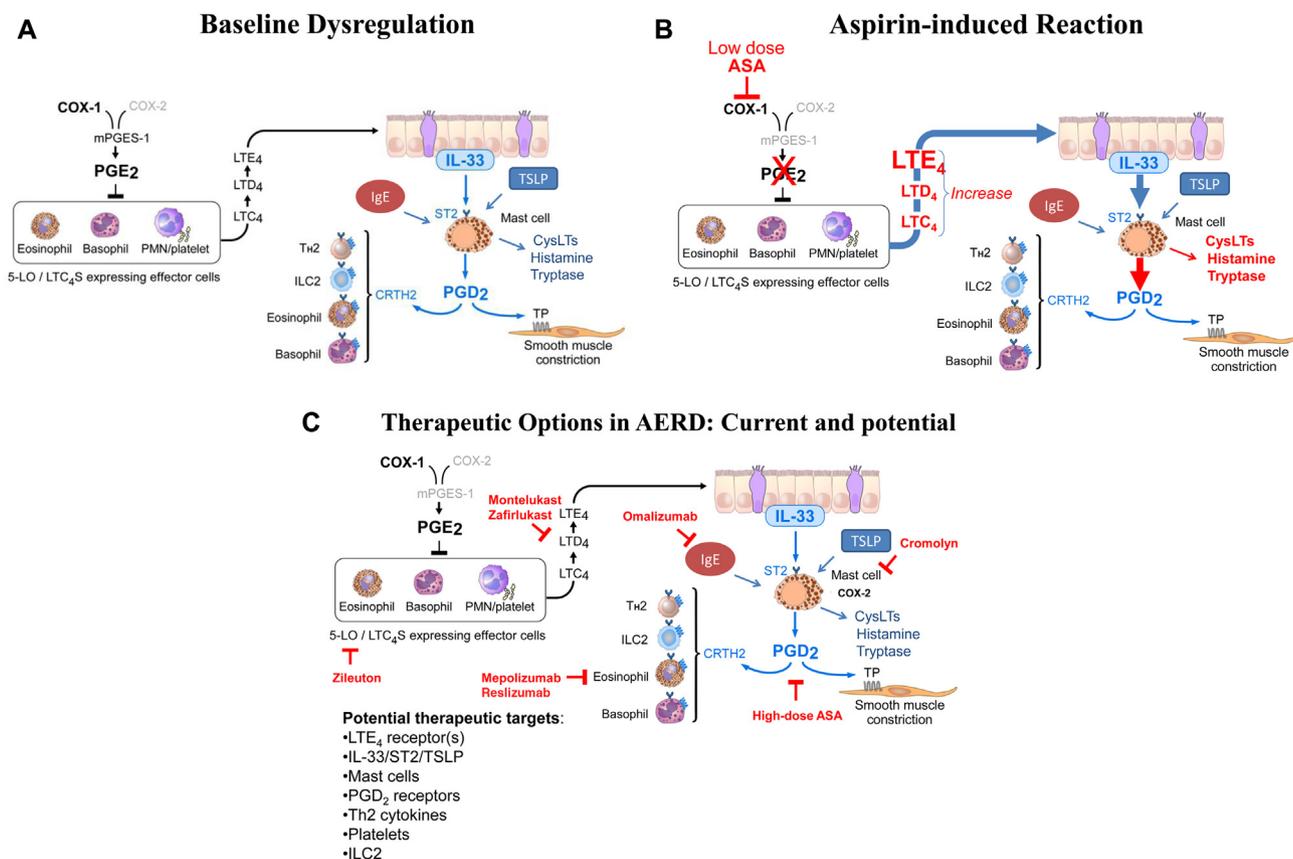


FIG 1. Current understanding of the mechanisms of AERD. **A**, Baseline LT and mast cell dysregulation. **B**, COX-1 inhibitor exposure leads to excessive mast cell mediator release. **C**, Available and potential therapeutic targets in patients with AERD informed by our current understanding of disease mechanism. ASA, Aspirin; CRTH2, prostaglandin D₂ receptor 2; ILC2, innate lymphoid type 2 cells; mPGES, microsomal PGE₂ synthase; TP, thromboxane receptor.

and decrease in blood eosinophil counts,⁷ with the latter suggesting a chemotactic effect mediated by D-prostanoid type 2 receptor/CRTH2. Patients with the largest quantities of urinary PGD₂ metabolites have nausea, abdominal pain, diarrhea, and skin rash that can limit their tolerance to aspirin desensitization.⁸ In contrast, subjects who tolerate desensitization show sharply reduced urinary levels of urinary PGD₂ metabolites on high-dose aspirin therapy compared with baseline (Fig 1, C).⁸

INNATE IMMUNE MECHANISMS

Despite the presence of IgE, mast cell activation, and severe type 2 immunopathology in patients with AERD, the inconsistent association with atopy argues for a prominent contribution from innate mechanisms. Innate type 2 immune responses involve structural cell-derived cytokines, such as IL-33 and thymic stromal lymphopoietin (TSLP; Fig 1, A). These cytokines can directly drive eosinophilic inflammation, mast cell activation, and IgE synthesis in the absence of adaptive immunity. The cleaved and activated form of TSLP is more abundant in nasal polyp tissues from patients with AERD than in aspirin-tolerant control subjects. Nasal polyp TSLP mRNA levels in polyps from patients with AERD correlate strongly with polyp hematopoietic PGD₂ synthase expression and baseline urinary PGD₂ metabolites.⁷ Nasal polyp tissue from patients with AERD also contains larger quantities of IL-33 protein than does tissue from

aspirin-tolerant control subjects. Moreover, AERD-like mice with a deletion of microsomal PGE₂ synthase display sharply increased lung IL-33 levels compared with wild-type control subjects.⁹ In the mouse a single injection of an mAb targeting IL-33 or blockade of the IL-33 receptor ST2 inhibits the aspirin-induced decrease in respiratory function, as well as the release of histamine, proteases, and the generation of PGD₂. Notably, in this model both basal IL-33 overexpression and reaction-induced IL-33 release depends partly on endogenous cysLTs, suggesting a potential mechanism that connects the proximal cysLT overproduction to the mast cell activation and persistent type 2 immunopathology in patients with AERD.

FUTURE TARGETS

Our understanding of AERD has expanded to include a greater understanding of mast cell activation at baseline and during aspirin-induced reactions. LTE₄, PGD₂, IgE, IL-33, and TSLP all have reported roles in human subjects and/or mouse models in this disease. A recent open-label study in the *Journal* showed that administration of humanized anti-IgE mAb (omalizumab) to patients with AERD sharply decreased the urinary levels of PGD₂ metabolites and LTE₄.¹⁰ The potential contributions of platelets and T prostanoid receptor are the focus of ongoing or recently completed trials ([clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01597375) #NCT01597375 and #NCT02216357). To date, no studies have assessed the effect of

targeting IL-33/ST2, TSLP, CysLT₂R, GPR99, or CRTH2 in patients with this disease (Fig 1, C). In the next 5 years, we should expect our therapeutic repertoire to expand, and with that will come further distillation of this fascinating disease process and a good chance of clinical benefit for our patients with AERD.

REFERENCES

1. Laidlaw TM, Boyce JA. Aspirin-exacerbated respiratory disease—new prime suspects. *N Engl J Med* 2016;374:484-8.
2. Cowburn AS, Sladek K, Soja J, Adamek L, Nizankowska E, Szczeklik A, et al. Overexpression of leukotriene C4 synthase in bronchial biopsies from patients with aspirin-intolerant asthma. *J Clin Invest* 1998;101:834-46.
3. Laidlaw TM, Kidder MS, Bhattacharyya N, Xing W, Shen S, Milne GL, et al. Cysteinyl leukotriene overproduction in aspirin-exacerbated respiratory disease is driven by platelet-adherent leukocytes. *Blood* 2012;119:3790-8.
4. Liu T, Laidlaw TM, Katz HR, Boyce JA. Prostaglandin E2 deficiency causes a phenotype of aspirin sensitivity that depends on platelets and cysteinyl leukotrienes. *Proc Natl Acad Sci U S A* 2013;110:16987-92.
5. Christie PE, Schmitz-Schumann M, Spur BW, Lee TH. Airway responsiveness to leukotriene C4 (LTC₄), leukotriene E4 (LTE₄) and histamine in aspirin sensitive asthmatic subjects. *Eur Respir J* 1993;6:1468-73.
6. Bankova LG, Lai J, Yoshimoto E, Boyce JA, Austen KF, Kanaoka Y, et al. Leukotriene E4 elicits respiratory epithelial cell mucin release through the G-protein-coupled receptor, GPR99. *Proc Natl Acad Sci U S A* 2016;113:6242-7.
7. Buchheit KM, Cahill KN, Katz HR, Murphy KC, Feng C, Lee-Sarwar K, et al. Thymic stromal lymphopoietin controls prostaglandin D2 generation in patients with aspirin-exacerbated respiratory disease. *J Allergy Clin Immunol* 2016;137:1566-76.e5.
8. Cahill KN, Bensko JC, Boyce JA, Laidlaw TM. Prostaglandin D(2): a dominant mediator of aspirin-exacerbated respiratory disease. *J Allergy Clin Immunol* 2015;135:245-52.
9. Liu T, Kanaoka Y, Barrett NA, Feng C, Garofalo D, Lai J, et al. Aspirin-exacerbated respiratory disease involves a cysteinyl leukotriene-driven IL-33-mediated mast cell activation pathway. *J Immunol* 2015;195:3537-45.
10. Hayashi H, Mitsui C, Nakatani E, Fukutomi Y, Kajiwara K, Watai K, et al. Omalizumab reduces cysteinyl leukotriene and 9alpha,11beta-prostaglandin F2 overproduction in aspirin-exacerbated respiratory disease. *J Allergy Clin Immunol* 2016;137:1585-7.e4.