



Cellular interactions in aspirin-exacerbated respiratory disease

Jana H. Badrani^a and Taylor A. Doherty^{a,b}

Purpose of review

The purpose of this review is to summarize the complex cellular interactions of aspirin-exacerbated respiratory disease (AERD) and how these interactions promote pathogenic mechanisms of AERD.

Recent findings

In addition to characteristic changes in eicosanoid levels, recent studies have identified increases in alarmin cytokines (IL-33, thymic stromal lymphopoietin) as well as activated innate lymphoid and plasma cell populations in samples from AERD patients.

Summary

Patients with AERD typically demonstrate high levels of proinflammatory eicosanoids including cysteinyl leukotrienes (CysLTs) and prostaglandin D₂ (PGD₂) and hyporesponsiveness to prostaglandin E₂ (PGE₂). CysLTs are released by mast cells, eosinophils, and adherent platelets and promote epithelial release of IL-33, which activates mast cells and group 2 innate lymphoid cells (ILC2s) in concert with CysLTs. TSLP induces PGD₂ release from mast cells which activates and recruits eosinophils, basophils, Th2 cells, and ILC2s via CRTH2. In turn, ILC2s and other cell types produce Th2 cytokines IL-4, IL-5, and IL-13 that, along with CysLTs and PGD₂, promote bronchoconstriction, eosinophilic tissue inflammation, and mucus production.

Keywords

aspirin-exacerbated respiratory disease, cysteinyl leukotrienes, eicosanoids, group 2 innate lymphoid cells, mast cells, prostaglandin D₂

INTRODUCTION

Aspirin-exacerbated respiratory disease (AERD) is a complex syndrome that results from dysregulated type 2 inflammation brought on by interactions between immune and structural cells. The classic ‘Samter’s Triad’ of AERD is characterized by asthma, chronic rhinosinusitis (CRS) with nasal polyposis (CRSwNP), and respiratory and other reactions to cyclooxygenase-1 (COX-1) inhibitors, such as aspirin and NSAIDs [1]. Symptoms after exposure to COX-1 inhibitors include nasal congestion, sneezing, rhinorrhea, bronchospasm, skin flushing, and hives [1]. AERD treatments include inhaled and systemic corticosteroids, leukotriene modifiers, aspirin desensitization, endoscopic sinus surgery, and possibly novel biologics targeting type 2 cytokines [1]. Aspirin desensitization has been observed to significantly reduce polyp recurrence, decrease symptoms and medication use, and is associated with improved quality of life [2]. AERD affects nearly 7% of asthmatic patients and is almost doubled in patients with severe asthma [3]. However, the prevalence of AERD may be underrepresented as a study of electronic health records of those exhibiting

characteristics of clinical AERD showed approximately 12% were undiagnosed [4]. An understanding of cellular and mediator mechanisms is critical for the development of future therapies for this debilitating syndrome.

MAJOR CELLULAR PLAYERS IN ASPIRIN-EXACERBATED RESPIRATORY DISEASE

Mast cells

Mast cell activation is central to AERD and patient samples have increased levels of proinflammatory cysteinyl leukotrienes (CysLTs), which contribute to mast cell activation. Canonical mast cell activation

^aDepartment of Medicine, University of California San Diego and ^bVeterans Affairs San Diego Healthcare System, La Jolla, California, USA

Correspondence to Taylor A. Doherty, MD, Department of Medicine, University of California San Diego, 9300 Campus Point Drive, MC 0678, La Jolla, CA 92037, USA. Tel: +1-858-822-7563; fax: +1 858 534 2110; e-mail: tdoherty@ucsd.edu

Curr Opin Allergy Clin Immunol 2021, 20:000–000

DOI:10.1097/ACI.0000000000000712

KEY POINTS

- AERD is characterized by an imbalance in eicosanoids, which influence how major cellular players including mast cells, eosinophils, epithelial cells, and ILC2s are regulated.
- Interactions between cells that produce PGD₂ and CysLTs and those that respond to these mediators are at the core of AERD.
- Epithelial release of alarmins IL-33 and TSLP activate ILC2s which is enhanced by CysLTs and PGD₂ from mast cells and eosinophils.
- Recent studies support a role for platelets and plasma cells in AERD pathogenesis.

involves FcεR1 triggering via IgE cross-linking, though mast cells are also activated using noncanonical mechanisms via the epithelial alarmin IL-33. Recently, IL-33 activation of mast cells was demonstrated to be dependent on the COX-1 pathway [5^{***}]. Mast cells also produce prostaglandin D₂ (PGD₂) in response to the epithelial alarmin thymic stromal lymphopoietin (TSLP) [6]. In fact, stimulation with TSLP and IL-33 increases PGD₂ production more than IL-33 alone, highlighting the potentiating effects of IL-33 and TSLP stimulation on mast cells. Mast cells also express and are activated through cysteinyl leukotriene 1 receptor (CysLT1R), which binds to LTC₄ and LTD₄, and less so to LTE₄. Prostaglandin E₂ (PGE₂), a metabolite of the COX pathway, binds to four different E-prostanoid receptors, E-prostanoid 1–4. Mast cells express E-prostanoid 2 and PGE₂ binding to E-prostanoid 2 decreases mast cell activation and inhibits the 5-LOX pathway and CysLT production [7].

The cyclooxygenase enzyme exists in two isoforms, COX-1 and COX-2, which converts arachidonic acid into Prostaglandin G₂ that is eventually processed into PGE₂, Prostaglandin F_{2α}, and PGD₂. Mast cells express COX-1 at baseline and upregulate expression of *Ptgs2* mRNA, which encodes for COX-2, after stimulation [8]. Patients with AERD demonstrate higher urinary PGD₂ metabolite compared with aspirin-tolerant controls and PGD₂ levels increased further during aspirin reactions [9]. As PGD₂ promotes bronchospasm and inflammatory cell recruitment, it is thus considered a dominant mediator produced by mast cells in AERD.

Eosinophils

Severe asthma associated with AERD is eosinophilic and nasal polyps from AERD patients have a greater number of eosinophils when compared with

samples from aspirin-tolerant patients [10]. Bronchial mucosal biopsies from patients with aspirin-intolerant asthma have been shown to have more eosinophils than those from patients with aspirin-tolerant asthma [11]. Further, elevated peripheral blood eosinophilia can also be observed in AERD patients when compared with aspirin-tolerant asthmatics and healthy controls [12].

Eosinophils express two high-affinity PGD₂ receptors: D-type prostanoid 1 and CRTH2 (D-type prostanoid 2). PGD₂ promotes eosinophil chemotaxis *in vitro* through CRTH2 and stimulation with a CRTH2-specific agonist increases eosinophil recruitment in models of allergic asthma and atopic dermatitis [13]. In addition to responding to PGD₂, eosinophils are also an important source of PGD₂ in AERD as hematopoietic Prostaglandin D synthase was found in higher amounts in AERD tissue and blood compared with non-AERD asthma controls [14,15]. In contrast to PGD₂, PGI₂ and PGE₂ play inhibitory roles in eosinophil responses through the prostacyclin receptor (IP) and PGE receptors E-prostanoid 2 and E-prostanoid 4, respectively [16]. Eosinophils cultured with NSAIDs produce CysLTs and Leukotriene B₄ which is ameliorated by E-prostanoid 2-mediated PGE₂ [17,18^{*}]. Although patients with AERD do not demonstrate changes in eosinophil E-prostanoid 4 expression, there is evidence that PGE₂-mediated inhibition as well as E-prostanoid 4 agonist-mediated inhibition of eosinophil chemotaxis is impaired in patients with AERD [19].

Eosinophils also likely play a role in AERD pathogenesis via interaction with epithelial cells [20]. Surfactant protein D (SPD) is a collectin protein that lines the airway epithelial cells and patients with AERD have been shown to have significantly lower serum SPD levels than those with aspirin-tolerant asthma. Eosinophils cultured with airway epithelial cells induce increases in α-smooth muscle actin expression, a feature of remodeling. SPD treatment, however, decreases the expression of eosinophil-induced α-smooth muscle actin [21]. Thus, SPD may mediate proremodeling features of eosinophils in AERD.

Group 2 innate lymphoid cells

Group 2 innate lymphoid cells (ILC2s) are a rare subset of lymphocytes that represent innate counterparts to Th2 cells. They express GATA binding protein 3 and, upon stimulation, produce large amounts of IL-4, IL-5, IL-9, IL-13, and the EGFR ligand amphiregulin. ILC2s are activated by epithelial cytokines IL-33, TSLP and IL-25 as well as modulated by eicosanoids including the CysLTs, PGD₂, PGI₂, and PGE₂ [22]. ILC2s were initially shown to

express CysLT1R and be activated by LTD₄ [23]. A recent report also showed that LTC₄ and LTE₄ increased eosinophilia in AERD-like prostaglandin synthase (*ptges*)^{-/-} mice via cysteinyl leukotriene 2 receptor (CysLT2R) regulation of IL-33 [24]. ILC2 activation by IL-33 is also potentiated by CysLTs through nuclear factor of activated T-cells signaling suggesting nonredundant pathways that drive ILC2 responses by lipid and cytokine mediators [25].

Several prostaglandins regulate ILC2 function providing potential insight into ILC2 function in AERD. Human ILC2s highly express CRTH2 and are activated by PGD₂ to induce chemotaxis and cytokine production [22,26,27]. In contrast, PGE₂ and PGI₂ play inhibitory roles in ILC2 responses. ILC2s express the E-prostanoid 2 and E-prostanoid 4 receptors, both of which may be required for PGE₂ to inhibit ILC2 function. Peripheral blood and tonsillar ILC2s cultured with PGE₂ had decreased GATA binding protein 3 expression, reduced type 2 cytokine production, and downregulated expression of the IL-2 receptor CD25 [27]. PGI₂ also inhibits the type 2 cytokine production in IL-33-stimulated ILC2s *in vitro* and *in vivo*. In an *Alternaria*-challenged mouse model, administration of PGI₂ significantly decreased the amount of lung type 2 cytokine-expressing ILC2s and airway eosinophilia [28]. In patients with AERD undergoing aspirin desensitization, ILC2s in nasal scrapings increased, whereas those in the blood decreased when compared with control patients. The increased tissue ILC2s were positively correlated with symptom scores during reactions. Consistent with previous studies, increases in urinary LTE₄ and PGD₂ metabolite were found during reactions [29]. Though the mechanism of recruitment of ILC2s to the airway in AERD is unknown, CysLTs and PGD₂ are likely candidates.

Epithelial cells

The epithelium and associated alarmins TSLP and IL-33 are likely central to AERD pathogenesis. TSLP activates mast cells to produce PGD₂ and epithelial cells release IL-33 in response to CysLT stimulation [6,30]. IL-33 is increased in nasal polyps from AERD patients and CysLT2R has been shown to be responsible for maximal IL-33 release in AERD-like mice [30,31]. Additionally, transcriptomic analysis of AERD nasal epithelial cells has revealed enriched expression of pathways involved in leukotriene metabolic processes as well as plasma membrane organization [32^{***}]. Folliculin is a protein expressed by epithelial cells to maintain epithelial cell integrity and survival. Patients with AERD had increased serum folliculin levels in comparison to aspirin-tolerant asthmatics and healthy controls.

Stimulating human airway epithelial cells with LTE₄ caused a significant increase in folliculin release. In the presence of LTE₄, folliculin knock-down reduced levels of IL-8 and occludin suggesting that folliculin may promote epithelial dysfunction in AERD [33].

Plasma cells

In CRSwNP, type 2 inflammation is associated with increased B cells, immunoglobins, and B-cell activating factor (BAFF). Nasal polyp tissue from patients with CRS contains increased levels of auto-antibodies, including IgG and IgA, in comparison to control tissue [34]. Further, higher concentrations of IgA, IgG, and IgE have been detected in patients with CRSwNP along with significantly higher numbers of naïve CD19⁺ B cells and plasma cells [35]. In a recent study, AERD sinus tissue was observed to have high IgE and IgG4 levels compared with non-AERD CRSwNP. Within the AERD patient population, patients with nasal polyp recurrence had higher IgE levels and polyp samples had higher numbers of IL-5Ra⁺ plasma cells compared with non-AERD CRSwNP [36^{***}].

The role of plasma cells and antibodies in AERD, particularly in nasal polyp formation, is currently unknown. Considering that AERD nasal polyps expressed more IL-5Ra⁺ plasma cells, plasma cell regulation via IL-5 may be of particular interest. ILC2s, Th2 cells and possibly mast cells produce IL-5 and could be functioning upstream to contribute to plasma cell activation in nasal polyps [36^{***}]. IgG4 and IgE production by plasma cells is also regulated by IL-4 and IL-13 signaling, which are two additional cytokines highly produced by ILC2s and Th2 cells, further highlighting a potential mechanism between these cells and plasma cell responses in AERD [37].

Platelets

Platelet adhesion to leukocytes may play an important role in AERD pathogenesis. Patients with AERD were shown to express higher levels of the activation marker P-selectin on platelets compared with aspirin-tolerant asthmatic controls [38]. Upon activation, platelets metabolize arachidonic acid into several different eicosanoids including PGD₂. Platelet PGD₂ is generated via the COX-1 isoform as platelets do not express the COX-2 isoform [39]. Importantly, peripheral blood from patients with AERD contains higher percentages of eosinophils, neutrophils, and monocytes with adherent platelets compared with aspirin-tolerant controls [40]. Platelets express elevated levels of LTC₄ synthase and

when activated neutrophils were combined with platelets, excess LTA_4 was converted to LTC_4 [39]. As neutrophils lack LTC_4 synthase and cannot metabolize LTA_4 into LTC_4 , the adherence of platelets to neutrophils allows for CysLT overproduction. To adhere to neutrophils and other granulocytes, platelets must be activated and express P-selectin or other adhesion molecules [14,39]. Thus, platelets likely contribute to both the overproduction of CysLTs and PGD_2 in AERD which can then further activate ILC2s and mast cells.

Other cells in aspirin-exacerbated respiratory disease

In contrast to IgE-mediated diseases such as allergic rhinitis, AERD is generally considered an antigen-independent type 2 inflammatory syndrome. However, T cells and upstream regulators are found in AERD samples. Patients with AERD have higher levels of IL-16 and thymus and activation-regulating cytokine (TARC) in nasal lavage samples compared with patients with allergic rhinitis and asthma [41]. TARC is the ligand for the C-C chemokine receptor type 4 receptor, is dominantly expressed on Th2 cells, and induces chemotaxis of Th2 cells [42]. Th2 cells also selectively express CRTH2 and are activated upon stimulation with PGD_2 to produce Th2 cytokines, though TCR cosignaling is required for full activation [43]. Interestingly, blood from aspirin-challenged patients with AERD were also observed to have higher baseline levels of CD4+CD25+CD127+ and CD4+CD45RA-CD45RO+ memory T cells and low baseline levels of CD4+CD25+CD127- cells. After aspirin challenge, there was an increase in the number of CD4+CD45RA-CD45RO+ memory T cells [43]. T-cell dysregulation in AERD is intriguing and perhaps staphylococcal superantigens promote broad T-cell responses though evidence is lacking that this occurs in AERD.

Basophils have also been implicated in AERD as nasal polyp tissue and peripheral blood from AERD patients contained more basophils than CRSwNP samples. One study found that nasal polyp basophils from patients with AERD expressed less 2D7, a granule content marker, which could be because of increased degranulation in AERD [44]. Further, basophils also express CysLT1R and CysLT2R and are activated by LTD_4 [45]. Patients with AERD and with aspirin-tolerant asthma have displayed significantly higher expression of the activation marker CD203c on basophils after stimulation with anti-IgE when compared with healthy controls. During aspirin challenges, patients with AERD had decreased peripheral blood CD203c-expressing basophils that

may be because of increased trafficking of basophils to target tissues [46]. Similar to other cells involved in AERD pathogenesis, basophils can produce CysLTs and PGD_2 , which could further regulate mast cell, Th2 cell, ILC2, and eosinophil activation.

Although AERD nasal polyps are primarily eosinophilic, neutrophils may be present in nasal polyp tissue [47]. Neutrophils metabolize LTA_4 to Leukotriene B4 via LTA_4 hydrolase, whereas other cells with the 5-LOX pathway will metabolize LTA_4 to LTC_4 via LTC_4S . LTC_4 can then be converted to the other CysLTs. As noted above, neutrophils adhered to platelets are able to function together to produce LTC_4 which is then metabolized to LTD_4 and LTE_4 [39].

MAJOR CELLULAR INTERACTIONS IN ASPIRIN-EXACERBATED RESPIRATORY DISEASE

Epithelium/mast cell/group 2 innate lymphoid cell interactions

Major cellular interactions in AERD are summarized in Fig. 1. Patients with AERD express higher levels of IL-33 in the basal layer of epithelial cells in nasal polyps. Similarly, the lungs of AERD-like *ptges*^{-/-} mice demonstrated increased expression of IL-33, especially after house dust mite treatment. Deletion of LTC_4 synthase in *ptges*^{-/-} mice decreased IL-33 levels in the lungs and decreased mast cell activation and eosinophilia [30]. This suggests that CysLTs regulate epithelial cell release of IL-33 which in turn can activate mast cells and ILC2s. Further, TSLP released from airway epithelial cells promotes PGD_2 production from mast cells which may also recruit and activate ILC2s, eosinophils, and other cell types [6].

Mast cell/eosinophil/group 2 innate lymphoid cell interactions

Many of the mediators characteristic of AERD, including PGD_2 , CysLTs, PGE_2 , and the epithelial alarmins, regulate ILC2 function [22]. ILC2s that express CRTH2, CysLT1R and ST2 (IL-33R) show potentiated activation upon stimulation with PGD_2 , CysLTs, and IL-33. Upon activation, ILC2s produce type 2 cytokines including IL-5 which is critical for recruitment, activation, and survival of eosinophils. Further, ILC2s produce IL-9 that can enhance the numbers of tissue mast cells. Eosinophils are activated by several mediators including PGD_2 , IL-5, IL-3, IL-33, and TSLP. Upon activation, eosinophils release CysLTs, PGD_2 , extracellular vesicles, and extracellular traps which further

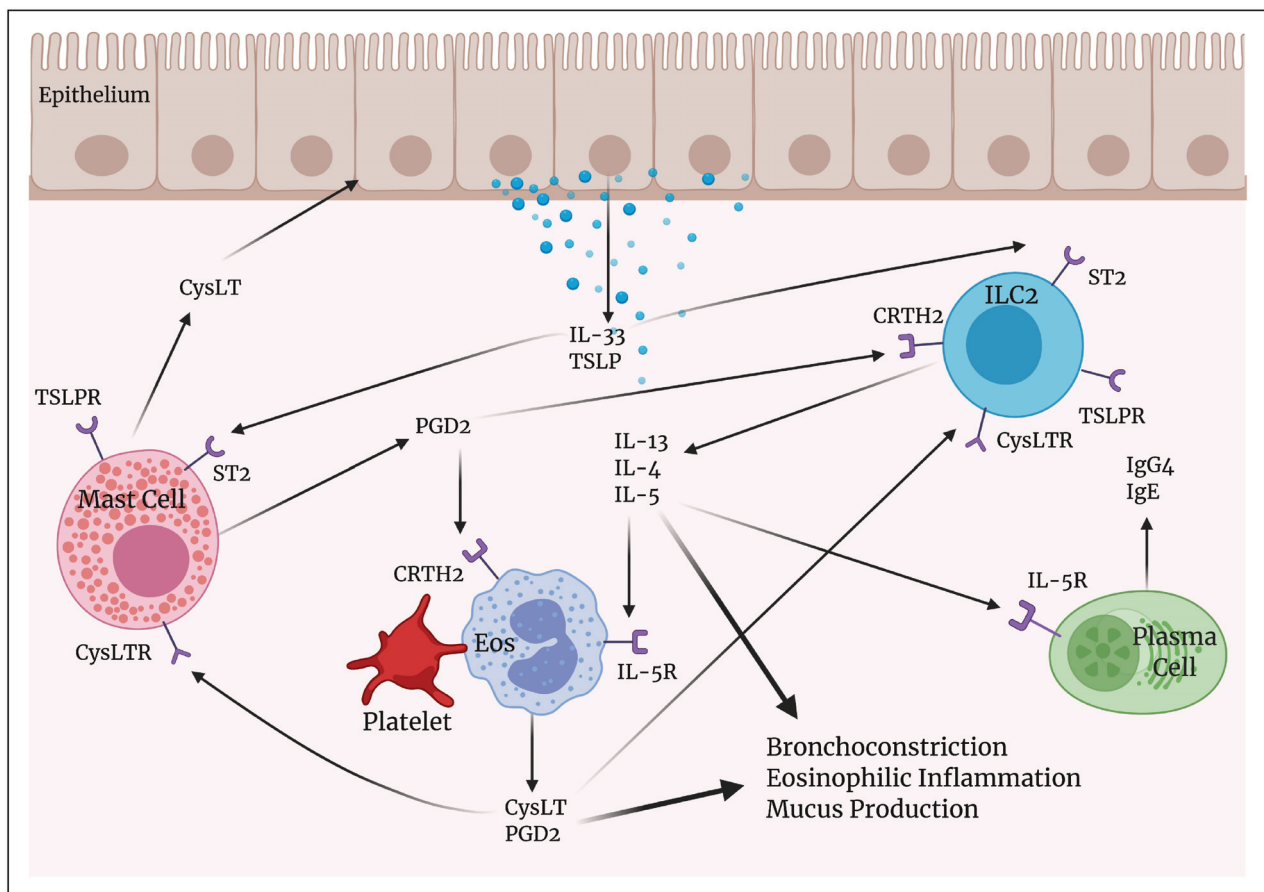


FIGURE 1. Major cellular interactions of AERD. CysLTs are released by mast cells and eosinophils and cause epithelial release of IL-33, which in turn activate mast cells, eosinophils, and ILC2s via ST2 (IL-33R). ILC2s release type 2 cytokines including IL-4, IL-5, and IL-13 which are capable of stimulating plasma cells to produce IgE and IgG4. IL-5 promotes recruitment, survival, and activation of eosinophils. Eosinophil activation is further promoted through direct interactions with platelets. These cells and mediators contribute overall to bronchoconstriction, eosinophilic inflammation, and mucus production that are features of AERD.

promote tissue damage and effector type 2 responses [20]. Eosinophil-produced PGD₂ and CysLTs in turn activate mast cells and ILC2s and are enhanced by epithelial cytokine costimulation. Thus, a complex interplay between many cell types through multiple mediators leads to pathologic features of AERD.

CONCLUSION

AERD is characterized by intense type 2 inflammation with the hallmarks of CRSwNP, moderate-to-severe asthma, and COX-1 inhibitor reactions. Samples from AERD patients show an imbalance in eicosanoids with high levels of proinflammatory mediators including CysLTs and PGD₂ and reduced responses to PGE₂. CysLTs are released by mast cells, eosinophils, basophils, and platelets and promote epithelial release of the alarmin IL-33 in AERD models. Further, epithelial TSLP induces mast cell activation and triggers the release of PGD₂, which can

then activate eosinophils, basophils, Th2 cells, and ILC2s via CRTH2. Novel insights into platelet and plasma cell responses as likely contributors to AERD has also been recently put forth. Importantly, the inclusion of the epithelial alarmins and novel cell types into our understanding of AERD is likely to have significant implications on future treatments.

Acknowledgements

Figure was created with BioRender.com.

T.A.D. is supported by Veterans Affairs BLR&D Award BX005073 and NIH grants AI 114585 and AI 070535.

Financial support and sponsorship

T.A.D. is supported by Veterans Affairs BLR&D Award BX005073 and NIH grants AI 114585 and AI 070535.

Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

1. Li KL, Lee AY, Abuzeid WM. Aspirin exacerbated respiratory disease: epidemiology, pathophysiology, and management. *Med Sci (Basel)* 2019; 7:45.
2. Mortazavi N, Esmailzadeh H, Abbasinazari M, *et al.* Clinical and immunological efficacy of aspirin desensitization in nasal polyp patients with aspirin-exacerbated respiratory disease. *Iran J Pharm Res* 2017; 16:1639–1647.
3. Rajan JP, Wineinger NE, Stevenson DD, White AA. Prevalence of aspirin-exacerbated respiratory disease among asthmatic patients: a meta-analysis of the literature. *J Allergy Clin Immunol* 2015; 135:676–681.e1.
4. Cahill KN, Johns CB, Cui J, *et al.* Automated identification of an aspirin-exacerbated respiratory disease cohort. *J Allergy Clin Immunol* 2017; 139:819–825.e6.
5. Pan D, Buchheit KM, Samuchiwal SK, *et al.* COX-1 mediates IL-33-induced extracellular signal-regulated kinase activation in mast cells: implications for aspirin sensitivity. *J Allergy Clin Immunol* 2019; 143:1047–1057.e8.
- This study demonstrated that mast cell COX-1 is required for IL-33-dependent eicosanoid release in mouse ex-vivo and in-vivo models and suggests a potential mechanism of aspirin desensitization.
6. Buchheit KM, Cahill KN, Katz HR, *et al.* Thymic stromal lymphopoietin controls prostaglandin D2 generation in patients with aspirin-exacerbated respiratory disease. *J Allergy Clin Immunol* 2016; 137:1566–1576.e5.
7. Wangberg H, White AA. Aspirin-exacerbated respiratory disease. *Curr Opin Immunol* 2020; 66:9–13.
8. Bando T, Fujita S, Nagano N, *et al.* Differential usage of COX-1 and COX-2 in prostaglandin production by mast cells and basophils. *Biochem Biophys Res* 2017; 10:82–87.
9. Cahill KN, Bensko JC, Boyce JA, Laidlaw TM. Prostaglandin D(2): a dominant mediator of aspirin-exacerbated respiratory disease. *J Allergy Clin Immunol* 2015; 135:245–252.
10. Payne SC, Early SB, Huyett P, *et al.* Evidence for distinct histologic profile of nasal polyps with and without eosinophilia. *Laryngoscope* 2011; 121:2262–2267.
11. Cowburn AS, Sladek K, Soja J, *et al.* Overexpression of leukotriene C4 synthase in bronchial biopsies from patients with aspirin-intolerant asthma. *J Clin Invest* 1998; 101:834–846.
12. Comhair SA, Bochenek G, Baicker-McKee S, *et al.* The utility of biomarkers in diagnosis of aspirin exacerbated respiratory disease. *Respir Res* 2018; 19:210.
13. Gervais FG, Cruz RP, Chateaufort A, *et al.* Selective modulation of chemokinesis, degranulation, and apoptosis in eosinophils through the PGD2 receptors CRTH2 and DP. *J Allergy Clin Immunol* 2001; 108:982–988.
14. Steinke JW, Payne SC, Borish L. Eosinophils and mast cells in aspirin-exacerbated respiratory disease. *Immunol Allergy Clin North Am* 2016; 36:719–734.
15. Feng X, Ramsden MK, Negri J, *et al.* Eosinophil production of prostaglandin D2 in patients with aspirin-exacerbated respiratory disease. *J Allergy Clin Immunol* 2016; 138:1089–1097.e3.
16. Peinhaupt M, Sturm EM, Heinemann A. Prostaglandins and their receptors in eosinophil function and as therapeutic targets. *Front Med (Lausanne)* 2017; 4:104.
17. Angulo EL, McKernan EM, Fichtinger PS, Mathur SK. Comparison of IL-33 and IL-5 family mediated activation of human eosinophils. *PLoS One* 2019; 14:e0217807.
18. Pal K, Ramsden M, Shim YM, *et al.* Suppression of aspirin-mediated eosinophil activation by prostaglandin E2: relevance to aspirin and nonsteroidal anti-inflammatory drug hypersensitivity. *Ann Allergy, Asthma Immunol* 2019; 123:503–506.
- This study demonstrated that human eosinophils treated with COX-1 inhibitors had increased leukotriene production that was inhibited by E-prostanoid 2 ligation.
19. Luschnig P, Frei R, Lang-Loidolt D, *et al.* Altered inhibitory function of the E-type prostanoid receptor 4 in eosinophils and monocytes from aspirin-intolerant patients. *Pharmacology* 2014; 94:280–286.
20. Choi Y, Lee Y, Park HS. Which factors associated with activated eosinophils contribute to the pathogenesis of aspirin-exacerbated respiratory disease? *Allergy Asthma Immunol Res* 2019; 11:320–329.
21. Choi Y, Lee DH, Trinh HK, *et al.* Surfactant protein D alleviates eosinophil-mediated airway inflammation and remodeling in patients with aspirin-exacerbated respiratory disease. *Allergy* 2019; 74:78–88.
22. Doherty TA, Broide DH. Airway innate lymphoid cells in the induction and regulation of allergy. *Allergol Int* 2019; 68:9–16.
23. Doherty TA, Khorram N, Lund S, *et al.* Lung type 2 innate lymphoid cells express cysteinyl leukotriene receptor 1, which regulates TH2 cytokine production. *J Allergy Clin Immunol* 2013; 132:205–213.
24. Liu T, Barrett NA, Kanaoka Y, *et al.* Type 2 cysteinyl leukotriene receptors drive IL-33-dependent type 2 immunopathology and aspirin sensitivity. *J Immunol* 2018; 200:915–927.
25. Lund SJ, Portillo A, Cavagnero K, *et al.* Leukotriene C4 potentiates IL-33-induced group 2 innate lymphoid cell activation and lung inflammation. *J Immunol* 2017; 199:1096–1104.
26. Xue L, Salimi M, Panse I, *et al.* Prostaglandin D2 activates group 2 innate lymphoid cells through chemoattractant receptor-homologous molecule expressed on TH2 cells. *J Allergy Clin Immunol* 2014; 133:1184–1194.
27. Doherty TA, Broide DH. Lipid regulation of group 2 innate lymphoid cell function: moving beyond epithelial cytokines. *J Allergy Clin Immunol* 2018; 141:1587–1589.
28. Zhou W, Toki S, Zhang J, *et al.* Prostaglandin I2 signaling and inhibition of group 2 innate lymphoid cell responses. *Am J Respir Crit Care Med* 2016; 193:31–42.
29. Eastman JJ, Cavagnero KJ, Deconde AS, *et al.* Group 2 innate lymphoid cells are recruited to the nasal mucosa in patients with aspirin-exacerbated respiratory disease. *J Allergy Clin Immunol* 2017; 140:101–108.e3.
30. Liu T, Kanaoka Y, Barrett NA, *et al.* Aspirin-exacerbated respiratory disease involves a cysteinyl leukotriene-driven IL-33-mediated mast cell activation pathway. *J Immunol* 2015; 195:3537–3545.
31. Drake LY, Kita H. IL-33: biological properties, functions, and roles in airway disease. *Immunol Rev* 2017; 278:173–184.
32. Teran Juarez LM, Vellore Sureshkumar P, Jimenez Chobillon A. Aspirin ■ exacerbated respiratory disease transcriptome analysis using RNA-seq. *Eur Respir J* 2019; 54:A5406.
- This study used RNA-seq to identify global transcriptomic differences in nasal epithelial cells from AERD and healthy controls. Their findings included major expression differences in genes related to plasma membrane organization, macroautophagy, and leukotriene metabolism.
33. Trinh HK, Pham DL, Choi Y, *et al.* Epithelial folliculin enhances airway inflammation in aspirin-exacerbated respiratory disease. *Clin Exp Allergy* 2018; 48:1464–1473.
34. Tan BK, Li QZ, Suh L, *et al.* Evidence for intranasal antinuclear autoantibodies in patients with chronic rhinosinusitis with nasal polyps. *J Allergy Clin Immunol* 2011; 128:1198–1206.e1.
35. Van Zele T, Gevaert P, Holtappels G, *et al.* Local immunoglobulin production in nasal polyposis is modulated by superantigens. *Clin Exp Allergy* 2007; 37:1840–1847.
36. Buchheit KM, Dwyer DF, Ordoñez-Montanes J, *et al.* IL-5Rα marks nasal ■ polyp IgG4- and IgE-expressing cells in aspirin-exacerbated respiratory disease. *J Allergy Clin Immunol* 2020; 145:1574–1584.
- This novel report demonstrated that AERD nasal polyps contained high levels of IgE and IgG4-expressing plasma cells. Further, single cell RNA-seq analysis showed that antibody-expressing cells from AERD nasal polyps had higher levels of the IL-5 receptor compared with non-AERD controls, and IL-5 treatment resulted in global expression changes.
37. Jeannin P, Lecoanet S, Delneste Y, *et al.* IgE versus IgG4 production can be differentially regulated by IL-10. *J Immunol* 1998; 160:3555.
38. Mitsui C, Kajiwara K, Hayashi H, *et al.* Platelet activation markers overexpressed specifically in patients with aspirin-exacerbated respiratory disease. *J Allergy Clin Immunol* 2016; 137:400–411.
39. Laidlaw TM, Boyce JA. Platelets in patients with aspirin-exacerbated respiratory disease. *J Allergy Clin Immunol* 2015; 135:1407–1414 quiz 1415.
40. Laidlaw TM, Kidder MS, Bhattacharyya N, *et al.* Cysteinyl leukotriene overproduction in aspirin-exacerbated respiratory disease is driven by platelet-adherent leukocytes. *Blood* 2012; 119:3790–3798.
41. Teran LM, Ramirez-Jimenez F, Soid-Raggi G, Velazquez JR. Interleukin 16 and CCL17/thymus and activation-regulated chemokine in patients with aspirin-exacerbated respiratory disease. *Ann Allergy, Asthma Immunol* 2017; 118:191–196.
42. Berin MC, Eckmann L, Broide DH, Kagnoff MF. Regulated production of the T helper 2-type T-cell chemoattractant TARC by human bronchial epithelial cells in vitro and in human lung xenografts. *Am J Respir Cell Mol Biol* 2001; 24:382–389.
43. Pezato R, Świerczyńska-Krępa M, Niżankowska-Mogilnicka E, *et al.* Systemic expression of inflammatory mediators in patients with chronic rhinosinusitis and nasal polyps with and without aspirin exacerbated respiratory disease. *Cytokine* 2016; 77:157–167.
44. Stevens W, Staudacher A, Poposki J, *et al.* Investigation of basophils in aspirin exacerbated respiratory disease pathogenesis. In: American Thoracic Society, editor. A93. Asthma breakthroughs: the role of the immune system in human asthma. American Thoracic Society International Conference Abstracts; 2019. p. A2370.
45. Gauvreau GM, Plitt JR, Baatjes A, MacGlashan DW. Expression of functional cysteinyl leukotriene receptors by human basophils. *J Allergy Clin Immunol* 2005; 116:80–87.
46. Mitsui C, Kajiwara K, Ono E, *et al.* Analysis of basophil activation in patients with aspirin-exacerbated respiratory disease. *J Allergy Clin Immunol* 2017; 140:1162–1164.e8.
47. Garcia Cruz ML, Jimenez-Chobillon MA, Teran LM. Rhinosinusitis and aspirin-exacerbated respiratory disease. *J Allergy (Cairo)* 2012; 2012:273752.