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Innate immune cell dysregulation drives inflammation and disease in Aspirin-Exacerbated Respiratory Disease

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Abstract

Aspirin exacerbated respiratory disease (AERD) is a complex inflammatory disorder that is not generally viewed as a disease involving the adaptive immune system but instead one largely driven by the innate immune system. This article focuses on the cellular dysregulation involving four central cell types: eosinophils, basophils, mast cells (MC), and innate lymphoid type 2 (ILC2) cells. AERD can be envisioned as involving a self-perpetuating vicious circle in which mediators produced by a differentiated activated epithelial layer, such as interleukin (IL)-25, IL-33, and thymic stromal lymphopoietin (TSLP) engage and activate each of these innate immune cells. The activation of these innate immune cells with their production of additional cytokine/chemokine and lipid mediators leads to further recruitment and activation of these innate immune cells. More importantly, numerous mediators produced by these innate immune cells provoke the epithelium to induce further inflammation. This self-perpetuating cycle of inflammation partially explains both current interventions suggested to ameliorate AERD (e.g., aspirin desensitization, leukotriene modifiers, anti-IL-5/IL-5 receptor, anti-IL-4 receptor, anti-IgE) and invites exploration of novel targets as specific therapies for this condition (prostaglandin D_2 antagonists or cytokine

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Conflict of Interest:

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antagonists (IL-25, IL-33, TSLP). Several of these interventions currently show promise in small retrospective analyses but now require definite clinical trials.

Keywords

Aspirin-exacerbated respiratory disease; mast cells; basophils; eosinophils; innate lymphoid cells; type 2 inflammation; IgE

Introduction:

Aspirin exacerbated respiratory disease (AERD) is a complex inflammatory disorder involving numerous cellular components of the immune system. While a discussion of all the myriad of immune cells and cellular mechanisms by which these cells become dysregulated is beyond the scope of this review, in this article we will focus on cellular dysregulation within the submucosal compartment and, specifically, the over-expression and dysregulation of four central cell types: eosinophils, basophils, mast cells (MC), and innate lymphoid type 2 (ILC2) cells (summarized in Table I).

Eosinophils

Eosinophils are potent type 2 inflammatory granulocytes associated with a variety of atopic and non-atopic conditions. In AERD, eosinophils are significantly elevated in the hyperplastic sinuses, nasal polyps (NPs), and lower airway when compared to healthy airway tissue.(1, 2) Likewise, levels of the eosinophil granule protein, eosinophil cationic protein (ECP), are also significantly elevated in NPs and lungs when compared to healthy controls.(3, 4) When assessing patients with NPs, studies are conflicting as to whether eosinophil numbers and ECP levels are similar (2, 3) or significantly elevated (1, 4) in AERD compared to aspirin-tolerant chronic rhinosinusitis with NPs (CRSwNP). This is mirrored by studies that differ as to whether mediators important in eosinophil survival and chemotaxis (*e.g.* interleukin (IL)-5, CCL11 (eotaxin-1)) are similar in both conditions (4, 5) or are significantly elevated in AERD.(3, 6, 7) The reported differences in eosinophils likely reflect the underlying heterogeneous endotypes observed among patient populations. CRSwNP is *predominantly* a type 2 inflammatory process in the US and Europe but many patients can have a type 1, type 3, or mixed inflammatory endotype (8, 9). Similarly, some patients with AERD have a non-type 2 inflammatory profile with enhanced numbers of neutrophils and reduced eosinophils (7, 10, 11). Higher levels of interferon (IFN)-γ have also been reported in NPs of a subset of patients with AERD (7, 12). Why certain patients develop a type 2 versus a non-type 2 inflammatory endotype remains unknown.

Eosinophils and lipid mediators.—Another outstanding question in AERD is how (or even if) eosinophils contribute to disease pathogenesis. Eosinophils are a source of prostaglandin D_2 (PGD_2)(13) and higher levels of the enzyme responsible for PGD_2 synthesis, PGDS, were reported in peripheral blood and NP eosinophils from patients with AERD.(14) Eosinophils are also capable of producing cysteinyl leukotrienes (CysLTs) and the key enzyme needed for CysLT production, LTC_4 synthase, was expressed in a significantly greater proportion of eosinophils in bronchial biopsies of patients with

AERD compared to aspirin-tolerant asthmatics (15). Furthermore, eosinophils can produce even higher levels of LTC_4 when primed with IL-5 or CCL11 (eotaxin), cytokines known to be elevated in AERD compared to healthy sinonasal tissue (16). Steinke and colleagues additionally found that $CD34^+$-derived eosinophils primed with IFN-γ release significantly higher levels of CysLTs following stimulation with PMA/ionomycin than those differentiated in media alone(12). Recent studies have also explored a relationship between platelets and eosinophils and found an increase in numbers of platelet-adherent eosinophils in patients with AERD compared to aspirin tolerant controls (17, 18). These adherent platelets can contribute to an over-production of CysLTs through an augmented transcellular conversion of leukotrienes (17, 18). Together, these findings suggest that eosinophils may be an important source of various lipid mediators known to be enhanced in AERD and thus could play a key role in driving disease pathogenesis (19, 20).

Eosinophils and fibrin formation.—In addition to their production of inflammatory mediators, eosinophils may also play a role in fibrin formation. Fibrin is the end-product following activation of the coagulation cascade and is elevated in NPs, serving to trap plasma proteins and promote mucosal edema (21). Takabayshi and colleagues found that eosinophils in AERD NPs expressed higher levels of L-plastin than in CRSwNP (22). L-plastin assists with the translocation of tissue factor to the surface of eosinophils. Elevated levels of L-plastin in AERD could in turn promote subsequent downstream activation of the coagulation cascade and lead to enhanced fibrin formation. However, more work is needed investigating the associations between L-plastin, coagulation factors, and fibrin in AERD.

Eosinophils and inflammation.—There are several other *in vitro* and *ex vivo* studies investigating eosinophils in CRSwNP that, while not performed in AERD specifically, provide insights into disease pathogenesis. For example, in patients with eosinophilic CRS, eosinophils were more activated in NPs than in blood as measured by intensity of CD69 surface expression (23). Activated eosinophils can then release granule proteins such as ECP and eosinophil-derived neurotoxin (EDN) which in turn have cytotoxic activity. EDN also upregulates matrix metallopeptidase-9 (MMP-9) expression in nasal epithelial cells which could in turn contribute to tissue remodeling (24). Finally, eosinophils are a major source of CLC protein/galectin-10 which is elevated in NPs and can contribute to both innate and adaptive inflammatory responses (25, 26). *In vitro* treatment of epithelial cells with CLC induced neutrophil chemotaxis as well as an up-regulation of several pro-inflammatory cytokines (25). Taken together, eosinophils are activated within NPs and their products likely contribute to epithelial barrier dysfunction as well as the generation of mixed inflammatory responses. However, future studies are needed to specifically reconfirm these observations in AERD.

Targeting eosinophils in AERD.—Daily aspirin maintenance therapy following an aspirin desensitization is an effective treatment option for patients with AERD (27). Cahill and colleagues found eosinophils were significantly higher in the peripheral blood following 8 weeks of daily aspirin therapy than before aspirin desensitization (28). This leads to the hypothesis that aspirin therapy may improve sinonasal disease by preventing the recruitment of circulating eosinophils to NPs. However, a separate study found that patients

with worsening clinical symptoms despite 4 weeks of daily aspirin therapy following desensitization had a significantly greater increase in peripheral blood eosinophils on therapy from baseline (210%) compared to patients who reported symptom improvement after 4 weeks of daily aspirin therapy (37%) (29). The mechanisms by which eosinophils increase in the circulation following aspirin therapy and the correlation with disease improvement (or worsening) over time warrants further investigation.

Corticosteroids (CCS) remain the first-line medical treatment for patients with CRSwNP (and AERD) and are known to reduce eosinophils (30, 31). However, it is unlikely that the clinical benefits of CCS are predominantly mediated solely through the reduction of eosinophils. Instead, benefits are likely mediated through a combination of this and their other anti-inflammatory effects including reduced inflammatory mediator release, decreased mucus secretion, reduced microvascular leak, and decreased epithelial remodeling.

Further support for eosinophils contributing to clinical disease are clinical trials of mepolizumab in CRSwNP. Mepolizumab, which binds soluble IL-5, significantly reduced both peripheral eosinophils and NP size compared to placebo-treated controls (32). While 17% of enrolled patients in this study had AERD, all received mepolizumab, so a *post-hoc* analysis specifically examining AERD patients could not be performed. Separately, a small retrospective single-site study of AERD patients found mepolizumab treatment was associated with improvement in nasal symptoms (33). Interestingly, mepolizumab did not prevent clinical symptoms from developing during aspirin desensitization (34). These findings suggest that eosinophils play a role in overall disease pathogenesis but potentially not during acute reactions to aspirin.

However, there is also evidence arguing against eosinophils contributing to NP pathogenesis. In patients with CRSwNP, treatment with dexpramipexole, a drug that depletes eosinophils by an unknown mechanism, led to a significant reduction in peripheral and NP eosinophils but produced no significant decrease in NP size or sinonasal symptoms.(35) In this study, only 3 patients (17%) had AERD so effects of dexpramipexole specifically in AERD could not be discerned. In a small case series examining 4 patients with AERD who had severe corticosteroid-dependent asthma, treatment with Mepolizumab was associated with poor asthma control albeit the authors did not evaluate sinonasal symptoms in these same patients (36). It is thus possible that targeting eosinophils may provide differential effects in the nose and lung, might not be effective in all patients with AERD, and that disease heterogeneity may exist among the population.

Finally, dupilumab is a monoclonal antibody that targets the IL-4 receptor α-chain and thereby blocks the downstream signaling of IL-4 and IL-13, that is effective in patients with AERD and CRSwNP (37, 38). While not specifically directed towards eosinophils, dupilumab was associated with a reduction in ECP, CCL26 (eotaxin-3), and IL-5 levels in nasal lavage fluid after 24 weeks of treatment (38). An increase in peripheral blood eosinophilia was noted with dupilumab, presumably reflecting the ability of dupilumab to inhibit the recruitment of eosinophils from the peripheral blood into NPs. However, patients with higher peripheral blood eosinophil counts (>300 cells/μL) did not have significantly better responses to dupilumab than patients with lower eosinophil counts (<300 cells/μL). It

has therefore been argued that other type 2 inflammatory cells and pathways may serve as the main targets of dupilumab.

In summary, eosinophils are elevated in patients with AERD and, in general, serve as a biomarker predictive of more severe sinonasal disease (39). *In vitro* studies have identified several mechanisms by which eosinophils could be contributing to pathogenesis, but *in vivo* studies have yet to conclusively confirm a specific role. Additionally, the majority of studies to date have focused on patients with CRSwNP, only a subset of which had AERD. As a result, it remains unclear if eosinophils play a distinct role in AERD in comparison to CRSwNP or, instead, have similar roles in all forms of (eosinophilic) CRS.

Basophils

Basophils represent another potent granulocyte subset that are important in a variety of type 2 respiratory disorders. Basophils were recently shown to be elevated in both NPs and peripheral blood of patients with AERD when compared CRSwNP (40). Interestingly, in this study, basophils in both AERD and CRSwNP were similarly activated, as noted by intensity of their CD63 surface expression. However, NP basophils demonstrated more extensive degranulation in AERD than in CRSwNP as measured by their loss in intracellular $2D7^+$ granules. There was a significant correlation between the loss of $2D7^+$ expression in basophils and overall sinonasal disease severity. Furthermore, analysis of microparticles (submicron-sized shed membrane vesicles released from activated or injured cells) from nasal lavage samples in patients with AERD demonstrated that basophils, MC and platelets were more highly activated in patients with AERD than in patient with CRS. These findings together suggesting basophils may be another important contributor to AERD pathogenesis (41).

Mast cells

Numerous observations suggest that MC play a central role in the pathogenesis of AERD. The pathology of AERD is characterized by an increased concentration of MC in NP and bronchial tissue compared to aspirin tolerant controls (42). While some older studies failed to directly demonstrate this increase in MCs using immunohistochemistry (IHC), even these studies did reliably demonstrate an increase in MC-derived-mediators—a phenomenon attributed to the inability to stain for activated, granule-depleted MCs (so-called “phantom” MCs)(43). This limitation of IHC was effectively overcome using both flow cytometry and targeted single-cell RNA sequencing, approaches that definitively identified increased MC numbers in AERD NP tissue relative to tissue samples obtained from aspirin tolerant asthmatics and normal controls (42). These techniques have also been used to characterize distinct populations of MC within NP tissue. While a population of MC unique to AERD was not found, local NP epithelial and subepithelial MC hyperplasia was more prominent in AERD NP when compared to non-AERD NP (44).

This increased MC burden occurs concomitantly with local accumulation of MC mediators, most notably CysLTs and prostaglandins, lipid mediators that as previously noted are critical to the pathogenesis of AERD. The constitutive overproduction of CysLTs in the resting state and the surge in CysLT production in response to non-selective non-steroidal

anti-inflammatory drugs (NSAIDs) is pathognomonic for AERD (43, 45). These elevated levels of CysLT in AERD reflects the increased expression of 5-lipoxygenase (5-LO) and leukotriene C_4 synthase (LTC_4S) in inflammatory cells including MC with, as previously noted, additional contributes from eosinophils and basophils (46). While these enzymes are expressed in several cell types, the elevation of other MC activation products, including tryptase, histamine, and PGD_2, as well as the surge of PGD2 and tryptase upon NSAID challenge suggest an important role for MC.(47) Attenuation of the bronchoconstriction associated with NSAID reactions by MC stabilizers further supports a central causative role for MC activation (47).

IgE and MC activation in AERD.—The mechanism of MC activation in AERD, however, is complex and is likely mediated by both IgE-dependent and -independent mechanisms. As is discussed in more detail elsewhere in this issue, levels of IgE in NP of patients with AERD are higher than in aspirin tolerant individuals and this includes both FcεRI-bound IgE (on MCs, basophils, and others) but also evidence for IgE being newly synthesized in the AERD tissue (48). The driving factors and targets of local IgE production are unclear but include IgE directed against the *staphylococcus aureus* enterotoxins that are prevalent in the CRS tissue. As many as 87% of patient with AERD are colonized with *Staph. aureus*, and levels of *Staph* superantigen-specific IgE are increased in AERD. Reflecting their role as both antigens (targeted by the IgE) but also as superantigens that drive non-specific T and B lymphocyte activation, *Staph aureus*-derived superantigens induce proliferation of polyclonal IgE within the polyp tissue, leading to chronic MC activation. There is a direct relationship between the level of IgE in polyp tissue and the speed of NP recurrence after surgery, further supporting the concept that local IgE contributes to the pathogenesis of AERD (49, 50). What is more controversial is the role of aeroallergens in AERD and, more specifically, aeroallergen-targeted IgE in driving MC activation. While AERD is associated with a high prevalence of sensitization to aeroallergens, it is unclear whether this is just the coincidental occurrence of allergic rhinitis in this condition or whether these aeroallergens play a direct pathogenic role. A role for inhaled aeroallergens seems implausible given the incapacity of these agents to access the sinonasal mucosa reflecting the usual severity of the extensive sinus hyperplastic tissue, occlusion of the sinus ostia, and severe nasal polyposis that categorize this condition. And while treatment of the allergic rhinitis as part of a comprehensive therapeutic approach to patients with AERD is recommended, further evidence against a meaningful causative role for aeroallergens is derived from the simple observation that an identical phenotype can develop in non-atopic individuals.

IgE Independent Mechanisms and AERD.—In addition to IgE, MC activation in AERD involves numerous IgE-independent mechanisms. One such mechanism reflects the ability of aspirin and NSAIDs themselves to directly trigger MC activation (51, 52). In these studies, both aspirin and NSAIDs directly stimulated MCs to initiate degranulation and arachidonate metabolic pathways.

Interestingly, and suggesting a feedforward pro-inflammatory cascade, in addition to their being a prominent MC product, CysLTs also act in an autocrine fashion to induce further

MC activation. Cysteinyl leukotriene receptors are expressed on MC and the direct effects of these CysLTs on MC activation have been demonstrated including via engagement of a recently described LTE_4 specific receptor (53–55).

In addition, decreased PGE_2 signaling on the anti-inflammatory EP2 receptor found on MC is also important for MC activation in AERD (3). NSAIDS decrease the production and release of PGE_2 from inflammatory cells. In combination with the baseline decreased expression of EP2 observed in AERD, the decrease in PGE_2, in response to ingestion of NSAIDs, releases the constraint that PGE_2/EP2 signaling provides and drives the surge in MC (and eosinophil) activation (56, 57). This role for PGE_2 has been verified by the ability of PGE_2 homologs to block reactions to NSAIDS in patient with AERD (58).

Lastly, innate cytokines, most notably IL-33, and TSLP have been implicated in non-IgE mediated MC activation (59). This has been best studied with regards to IL-33 which can stimulate both eicosanoid generation and type 2-cytokine production by MC (60).

Together, these observations regarding MC behavior can explain the paradoxical contrasting actions of aspirin in AERD. Thus, initially aspirin (and other NSAIDs) drive the anaphylactoid response via inhibition of PGE_2 expression and loss of constraints on MCs leading to the observed surge of MC-derived PGD_2 and tryptase. But longer-term administration of high dose aspirin after desensitization leads to decreased COX activity, thereby blocking both IL-33-associated COX-1-dependent MC activation and COX-2-dependent generation of PGD_2. MC derived PGD_2 is a central mediator in AERD through its importance in the chemotaxis and activation of eosinophils, basophils, Th2 lymphocytes, and, in particular, ILC2s, as discussed below (19). This putative importance of PGD_2 is supported by observations that the clinical improvement of AERD after aspirin desensitization correlates with a striking decrease in expression of MC (and eosinophil)-derived PGD_2 (28). Although CysLT production increases after aspirin desensitization, end organ reactivity, at least to LTE_4, is drastically attenuated after aspirin desensitization, arguing that CysLTs and PGD_2 are important in the pathophysiology of AERD (61).

In addition to a putative role in targeting MCs as the mechanism of aspirin desensitization, additional arguments supporting a central role for MCs in AERD is derived from experience with biologics. Omalizumab improves sinonasal symptoms in AERD and this occurs in association with decreases in the urinary PGD_2 metabolite and LTE_4 levels (62–64). This argues not only for a role for MCs in AERD but presumably for MC- (and basophil)-associated IgE, albeit IgE that is directed against an unknown antigen. In addition, mepolizumab and dupilumab, as previously noted, have both demonstrated benefit in AERD (33, 37). While both agents target tissue eosinophilia, dupilumab, unlike mepolizumab, has also both been shown to target local IgE-producing cells in NP to inhibit local IgE production (37, 65). And dupilumab has direct inhibitory effects on MCs as well. The argument that the beneficial effects of these biologics reflect their targeting of IgE-MCs rather than tissue eosinophilia in AERD includes the dexpramipexole study discussed above. Interestingly, this treatment while largely eliminating tissue eosinophils was associated with increases in MC numbers (35). Finally, imatinib, a MC-depleting tyrosine kinase inhibitor, was shown to improve lung function and airway reactivity in a population of

severe asthmatics and this occurred in association with MC depletion. This observation invites investigation into the benefits of imatinib in as a therapeutic option in AERD (66).

Group 2 Innate Lymphoid Cells (ILC2s)

ILC2s are a recently discovered subset of lymphocytes that lack T cell receptors and represent the innate counterparts to adaptive T helper (T_H) 2 cells with similar transcription factors and cytokines (67). Airway ILC2s have been implicated in AERD as they are recruited to the airway in AERD patients and are modulated by lipids and cytokines central to AERD pathogenesis.(68) During COX-1 inhibitor challenge/desensitization in AERD patients, accumulation of ILC2s in the nasal mucosa occurred along with concurrent reduction of ILC2s in the blood, suggesting that ILC2s migrate from the blood to the nose in the setting of COX-1 inhibition in AERD (68). Nasal ILC2s also correlated with increased reaction severity, and similar to other studies, elevated urinary PGD_2 metabolite and LTE_4 concentrations were found at the time of reactions. Higher ILC2 levels are also detected in eosinophilic NP compared to non-eosinophilic polyps and other tissues (69–71). Recently, ILC2s from the polyps of those with CRS have shown increased cytokine expression and loss of steroid responsiveness compared with blood ILC2s (72). Thus, ILC2s are well positioned in the airways of AERD patients with eosinophilic nasal polyposis to propagate the type 2 inflammation that is characteristic of AERD.

ILC2s in type 2 inflammation.—Similar to adaptive $CD4^+$Th2 cells, ILC2s express the transcriptional regulator GATA-3 and when stimulated, produce IL-4, IL-5, and IL-13 which leads to tissue eosinophilia, mucus production, airway hyperresponsiveness, and promotion of adaptive Th2 and IgE responses (67). Animal models have shown that ILC2s are critical to lung eosinophilia, mucus production and hyperresponsiveness in response to viruses and allergens, independent of T and B cells (reviewed in (73)). Human studies have further validated that airway ILC2s are increased in patient samples from those with eosinophilic nasal polyposis (69–71) and oral steroid-dependent asthma (74, 75). As AERD is considered an antigen-independent disorder with dysregulated eicosanoid pathways, ILC2s that are activated by cytokines and lipids (and not directly by antigens) could promote the eosinophilic CRSwNP and moderate-to-severe asthma in AERD.

ILC2 regulation by lipid mediators.—ILC2s are activated by lipid mediators including PGD_2 and CysLTs as well as by innate cytokines known as “alarmins” which include IL-33, IL-25, and thymic stromal lymphopoietin (TSLP)(67, 76). Importantly, stimulation of ILC2s with CysLTs or PGD_2 potently induces secretion of IL-4, in addition to IL-5 and IL-13, compared to IL-33 which induces minimal IL-4 production from ILC2s (77–79). Combined lipid mediator and cytokine stimulation, as is present in type 2 inflammation, further enhances ILC2 activation compared with individual mediators by themselves (78, 80, 81).

Leukotriene pathway dysfunction in AERD has been well studied and high production of CysLTs that include LTC_4, LTD_4, and LTE_4 has been demonstrated. AERD patients display higher levels of nasal 5-LO and LTC_4 and, as previously noted, have elevated baseline urinary levels of LTE_4 as well as LTB_4 (45, 82). First discovered in mice, ILC2s were shown

to express CysLT1Rs and are potently activated by LTD_4 *in vivo* and *in vitro* to produce Th2 cytokines (77). CysLT2R has also been implicated to promote ILC2 expansion through LTC_4-driven IL-33 production by alveolar type 2 cells in AERD murine models (83). In humans, the terminal and most stable CysLT, LTE_4 most potently promoted ILC2 survival and cytokine release (81). Thus, CysLTs which are central to AERD pathogenesis are also potent activators of ILC2s.

The role of PGD2 in AERD is of exceptional focus given its downstream effects including bronchospasm and immune cell activation, as well as increased production in patients refractory to desensitization and severe asthma (19, 84). PGD_2 potently activates and induces migration of ILC2s through binding of chemoattractant receptor-homologous molecule expressed on T_H2 cells (CRTH2) which is often used to identify human ILC2s after lineage exclusion (78, 85). Interestingly, a recent report showed that ILC2-endogenous production of PGD_2 promotes ILC2 cytokine production in the presence of epithelial cytokines suggesting that the PGD_2 burden from other cell types including eosinophils and MCs may only compound the influence of endogenous ILC2 PGD_2 production (86).

In contrast to CysLTs and PGD_2, PGE_2 and PGI_2 play inhibitory roles in ILC2 responses (87, 88). Similar to the its previous noted inhibitor effects on MCs, PGE_2 suppresses human ILC2 responses through the activation of EP2 and EP4 receptors found on ILC2s (87). In patients with AERD, PGE_2 expression is decreased and tissue resistance to PGE_2 is present that leads to reduced inhibition of leukotriene production resulting in increased LTB_4 and CysLTs (89–92). Similarly, PGI_2 suppresses human ILC2 production of type 2 cytokines and administration of PGI_2 decreases lung ILC2 responses in mice (88). Overall, eicosanoids relevant to AERD pathogenesis have direct effects on ILC2 recruitment, activation, and expansion which could contribute to the pathogenetic manifestations of the disease.

ILC2 activation by epithelial cytokines.—Epithelial-derived cytokine “alarmins” include IL-33, IL-25, and TSLP and were the first mediators shown to activate ILC2s (reviewed in (67, 73)). Human ILC2s were initially found to produce Th2 cytokines after stimulation with IL-33 and TSLP *in vitro*, and TSLP-induced ILC2 responses were demonstrated to be dependent on the transcription factor GATA3 (93, 94). Importantly, TSLP promotes CCS resistance in ILC2s and a recent report showed that ILC2s activated by epithelial alarmins switch from resting $CD45RA^+$ ILC2s to CCS-resistant $CD45RO^+$ ILC2s which correlate with increased disease severity in CRS patients (72, 75). Interestingly, though AERD is largely considered a disorder of eicosanoid dysregulation, epithelial alarmins IL-33 and TSLP may contribute to pathogenesis through multiple upstream and downstream mechanisms involving MCs and lipid mediators (60, 95, 96). IL-25 levels are also higher in plasma of AERD patients compared to controls and IL-25 release from epithelial-associated chemosensory brush cells may specifically activate ILC2s through a CysLT pathway (97, 98). Taken together, the abnormal lipid and epithelial cytokine pathway activation found in AERD may work in concert to promote ILC2 responses and type 2 inflammation.

Tissue trafficking of ILC2s.—Though initial ILC2 paradigms largely suggested that local proliferation is the dominant mechanism of accumulation in tissues, it is clear that

ILC2 trafficking contributes critically during type 2 inflammation (99). ILC2s display increased migration during inflammatory conditions including during COX-1 inhibitor challenge in AERD (68, 99). In particular, increased *ex vivo* chemotaxis of ILC2 cells to PGD_2 has been demonstrated in patients with asthma and allergy compared to controls and is dependent on CRTH2 expression (78, 85, 100). Further, airway PGD_2 challenges in mice directly induces peripheral ILC2 trafficking to the lungs (101). CysLTs and less so IL-25 and IL-33 also induce migration of human ILC2s *in vitro* which could be relevant to ILC2 trafficking in AERD (78, 81).

Targeting of ILC2s in AERD.—Many of the therapeutics utilized in AERD treatment mechanistically target ILC2s. ß2-adrenergic receptors are found on lung ILC2s and ß-agonist treatment results in decreased ILC2 numbers (102). The CysLT1R antagonist montelukast also inhibits CysLT-induced ILC2 cytokine production (77, 80). A diet rich in omega-3s may also suppress ILC2s as demonstrated in a murine study and has been studied with some efficacy in AERD.(103, 104) Newer biologics targeting ILC2 pathways include inhibition of upstream mediators including an anti-TSLP antibody (105), a GATA-3 inhibitor (106) as well as antibodies blocking the downstream ILC2-produced cytokines IL-4, IL-5 and IL-13. These strategies could be useful in dampening the effects of type 2 inflammation in AERD through suppression ILC2 responses (107–111).

Conclusion:

This review has focused on the key roles for several cells of the innate immune system, specifically on the roles of eosinophils, basophils, MCs, and ILC2s in the pathogenesis of AERD. It is unlikely that any one of these cells is solely responsible for the pathogenesis of AERD. As such, a highly focused intervention targeting any single immune cell is unlikely to produce a comprehensive disease remission. It is also important to appreciate the synergistic upregulatory pathogenic interaction of all of these cells with sinonasal epithelial cells (figure 1). It is easy to envision a self-perpetuating vicious circle emerging in which alarmins produced by activated epithelial cells, such as IL-25, IL-33, and TSLP can engage and activate each of these innate immune cells. And in turn, activation of these cells with production of additional alarmins and lipid mediators leads to further recruitment and activation of each these innate immune cells. More importantly, production of numerous mediators by these cells produces a feedback loop leading to the continuing and worsening inflammation being induced by epithelial cells. In particular, several mediators. but especially IL-13, are central in driving the capacity of epithelial cells to produce T2 inflammation-inducing cytokines/chemokines and lipid mediators. And, these actions on epithelial cells further drives their differentiation into goblet cells and, most importantly, IL-25-producing chemosensory cells (112). While this model does not explain the initial pathogenic “hit” initiating AERD. what is remarkable is that the perpetuation and progression of this disease can be seen as persisting even in the absence of engagement by antigen of the adaptive immune system (T or B cells). Fortunately, the models discussed throughout this paper explain both current interventions either proven or suggested to specifically ameliorate AERD (e.g., aspirin desensitization, anti-IL-5/IL-5R, anti-IL-4R, anti-IgE) and invite novel targets for exploration as specific therapies for this condition

(PGD_2/CRTH antagonists or cytokine antagonists (IL-25, IL-33, TSLP). Several of these interventions already show promise is small retrospective analyses and now require definite clinical trials.

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Glossary:

Alarmins
Molecules, such as cytokines, that are released from damaged or necrotic cells to induce immune responses

Autocrine signaling
A form of cell signaling in which a cell releases a hormone or other soluble mediator that binds to receptors on the same cell

Chemotaxis
the movement of a cell in response to a concentration gradient of a particular substance

Eicosanoids
Pro-inflammatory cell signaling lipid molecules that are derived from arachidonic acid. Examples of eicosanoids include prostaglandins, leukotrienes, and thromboxanes

Endotype
A subtype of a disease condition which is caused by a distinct functional or pathophysiological mechanism

Fc epsilon RI (FcεRI)
The high-affinity receptor for the Fc region of Immunoglobulin E (IgE). Cross-linking of FcεRI with IgE leads to degranulation and inflammatory mediate release from mast cells and basophils

Leukotrienes
Soluble lipid mediators that are generated from arachidonic acid by lipoxygenase enzymes and serve as important inflammatory mediators

Metaplastic transformation
the transformation from one differentiated cell type to another differentiated cell type

Prostaglandins
Soluble lipid mediators that are generated from arachidonic acid by cyclooxygenase enzymes and help generate inflammatory responses

Superantigens
A class of antigens that cause non-specific polyclonal T cell activation and massive cytokine release, leading to excess adaptive immunity

Tissue Factor
A cell surface glycoprotein that initiates blood coagulation cascades by inducing the formation of thrombin

Abbreviations

AERD	aspirin-exacerbated respiratory disease
CCS	corticosteroids
CLC	Charcot-Leyden crystal
COX	cyclooxygenase
CRS	chronic rhinosinusitis
CRTH2	chemoattractant receptor-homologous molecule expressed on T_H2 cells
CysLT	cysteinyl leukotriene
ECP	eosinophil cationic protein
EDN	eosinophil-derived neurotoxin
EPX	eosinophil peroxidase
IFN	interferon
IHC	immunohistochemistry
IL	interleukin
ILC2	innate lymphoid type 2 cell
LTC_4S	leukotriene C_4 synthase
5-LO	5-lipoxygenase
LT	leukotriene
MBP	major basic protein
MC	mast cells
NP	nasal polyps
NSAID	non-steroidal anti-inflammatory drug
PG	prostaglandin
T_H	T helper
RANTES	regulated upon activated, normal T cell expressed and presumably secreted

TSLP	thymic stromal lymphopoietin

References

1. Payne SC, Early SB, Huyett P, Han JK, Borish L, Steinke JW. Evidence for distinct histologic profile of nasal polyps with and without eosinophilia. Laryngoscope. 2011;121(10):2262–7. [PubMed: 21898422]
2. Mahdavinia M, Carter RG, Ocampo CJ, Stevens W, Kato A, Tan BK, et al.Basophils are elevated in nasal polyps of patients with chronic rhinosinusitis without aspirin sensitivity. J Allergy Clin Immunol. 2014;133(6):1759–63. [PubMed: 24636088]
3. Perez-Novo CA, Watelet JB, Claeys C, Van Cauwenberge P, Bachert C. Prostaglandin, leukotriene, and lipoxin balance in chronic rhinosinusitis with and without nasal polyposis. J Allergy Clin Immunol. 2005;115(6):1189–96. [PubMed: 15940133]
4. Stevens WW, Ocampo CJ, Berdnikovs S, Sakashita M, Mahdavinia M, Suh L, et al.Cytokines in Chronic Rhinosinusitis. Role in Eosinophilia and Aspirin-exacerbated Respiratory Disease. Am J Respir Crit Care Med. 2015;192(6):682–94. [PubMed: 26067893]
5. Olze H, Forster U, Zuberbier T, Morawietz L, Luger EO. Eosinophilic nasal polyps are a rich source of eotaxin, eotaxin-2 and eotaxin-3. Rhinology. 2006;44(2):145–50. [PubMed: 16792175]
6. Steiner UC, Bischoff S, Valaperti A, Ikenberg K, Starzyk J, Bucher S, et al.Endotypes of chronic rhinosinusitis with nasal polyps with and without NSAID aeuro" intolerance. Rhinology. 2020;58(6):544–9. [PubMed: 32692786]
7. Scott WC, Cahill KN, Milne GL, Li P, Sheng Q, Huang LC, et al.Inflammatory heterogeneity in aspirin-exacerbated respiratory disease. J Allergy Clin Immunol. 2020.
8. Tomassen P, Vandeplas G, Van Zele T, Cardell LO, Arebro J, Olze H, et al.Inflammatory endotypes of chronic rhinosinusitis based on cluster analysis of biomarkers. J Allergy Clin Immunol. 2016;137(5):1449–56e4. [PubMed: 26949058]
9. Stevens WW, Peters AT, Tan BK, Klingler AI, Poposki JA, Hulse KE, et al.Associations Between Inflammatory Endotypes and Clinical Presentations in Chronic Rhinosinusitis. J Allergy Clin Immunol Pract. 2019;7(8):2812–20e3. [PubMed: 31128376]
10. Jakiela B, Soja J, Sladek K, Przybyszowski M, Plutecka H, Gielicz A, et al.Heterogeneity of lower airway inflammation in patients with NSAID-exacerbated respiratory disease. J Allergy Clin Immunol. 2020.
11. Celejewska-Wojcik N, Wojcik K, Ignacak-Popiel M, Cmiel A, Tyrak K, Gielicz A, et al.Subphenotypes of nonsteroidal antiinflammatory disease-exacerbated respiratory disease identified by latent class analysis. Allergy. 2020;75(4):831–40. [PubMed: 31803947]
12. Steinke JW, Liu L, Huyett P, Negri J, Payne SC, Borish L. Prominent role of IFN-gamma in patients with aspirin-exacerbated respiratory disease. J Allergy Clin Immunol. 2013;132(4):856–65e1–3. [PubMed: 23806637]
13. Luna-Gomes T, Magalhaes KG, Mesquita-Santos FP, Bakker-Abreu I, Samico RF, Molinaro R, et al.Eosinophils as a novel cell source of prostaglandin D2: autocrine role in allergic inflammation. J Immunol. 2011;187(12):6518–26. [PubMed: 22102725]
14. Feng X, Ramsden MK, Negri J, Baker MG, Payne SC, Borish L, et al.Eosinophil production of prostaglandin D2 in patients with aspirin-exacerbated respiratory disease. J Allergy Clin Immunol. 2016;138(4):1089–97e3. [PubMed: 27423494]
15. 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. [PubMed: 9466979]
16. Bandeira-Melo C, Weller PF. Eosinophils and cysteinyl leukotrienes. Prostaglandins Leukot Essent Fatty Acids. 2003;69(2–3):135–43. [PubMed: 12895596]
17. 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(16):3790–8. [PubMed: 22262771]

18. Mitsui C, Kajiwara K, Hayashi H, Ito J, Mita H, Ono E, et al.Platelet activation markers overexpressed specifically in patients with aspirin-exacerbated respiratory disease. J Allergy Clin Immunol. 2016;137(2):400–11. [PubMed: 26194538]
19. 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(1):245–52. [PubMed: 25218285]
20. Miyata J, Fukunaga K, Kawashima Y, Watanabe T, Saitoh A, Hirosaki T, et al.Dysregulated fatty acid metabolism in nasal polyp-derived eosinophils from patients with chronic rhinosinusitis. Allergy. 2019;74(6):1113–24. [PubMed: 30667533]
21. Takabayashi T, Kato A, Peters AT, Hulse KE, Suh LA, Carter R, et al.Excessive fibrin deposition in nasal polyps caused by fibrinolytic impairment through reduction of tissue plasminogen activator expression. Am J Respir Crit Care Med. 2013;187(1):49–57. [PubMed: 23155140]
22. Takabayashi T, Tanaka Y, Susuki D, Yoshida K, Tomita K, Sakashita M, et al.Increased expression of L-plastin in nasal polyp of patients with nonsteroidal anti-inflammatory drug-exacerbated respiratory disease. Allergy. 2019;74(7):1307–16. [PubMed: 30479022]
23. Yun Y, Kanda A, Kobayashi Y, Van Bui D, Suzuki K, Sawada S, et al.Increased CD69 expression on activated eosinophils in eosinophilic chronic rhinosinusitis correlates with clinical findings. Allergol Int. 2020;69(2):232–8. [PubMed: 31928947]
24. Tsuda T, Maeda Y, Nishide M, Koyama S, Hayama Y, Nojima S, et al.Eosinophil-derived neurotoxin enhances airway remodeling in eosinophilic chronic rhinosinusitis and correlates with disease severity. Int Immunol. 2019;31(1):33–40. [PubMed: 30239772]
25. Delemarre T, Holtappels G, De Ruyck N, Zhang N, Nauwynck H, Bachert C, et al.Type 2 inflammation in chronic rhinosinusitis without nasal polyps: Another relevant endotype. J Allergy Clin Immunol. 2020;146(2):337–43e6. [PubMed: 32417132]
26. Persson EK, Verstraete K, Heyndrickx I, Gevaert E, Aegerter H, Percier JM, et al.Protein crystallization promotes type 2 immunity and is reversible by antibody treatment. Science. 2019;364(6442).
27. Stevens WW, Jerschow E, Baptist AP, Borish L, Bosso JV, Buchheit KM, et al.The role of aspirin desensitization followed by oral aspirin therapy in managing patients with aspirin-exacerbated respiratory disease: A Work Group Report from the Rhinitis, Rhinosinusitis and Ocular Allergy Committee of the American Academy of Allergy, Asthma & Immunology. J Allergy Clin Immunol. 2021;147(3):827–44. [PubMed: 33307116]
28. Cahill KN, Cui J, Kothari P, Murphy K, Raby BA, Singer J, et al.Unique Effect of Aspirin Therapy on Biomarkers in Aspirin-exacerbated Respiratory Disease. A Prospective Trial. Am J Respir Crit Care Med. 2019;200(6):704–11. [PubMed: 30978291]
29. Jerschow E, Edin ML, Pelletier T, Abuzeid WM, Akbar NA, Gibber M, et al.Plasma 15-Hydroxyeicosatetraenoic Acid Predicts Treatment Outcomes in Aspirin-Exacerbated Respiratory Disease. J Allergy Clin Immunol Pract. 2017;5(4):998–1007e2. [PubMed: 28159558]
30. Suzuki N, Ko-Mitamura EP, Inui T, Terada T, Dejima K, Nagata N, et al.Steroids Inhibit Eosinophil Accumulation and Downregulate Hematopoietic Chemotaxic Prostaglandin D2 Receptor in Aspirin-Exacerbated Respiratory Disease. Ear Nose Throat J. 2020:145561320902858.
31. Orlandi RR, Kingdom TT, Smith TL, Bleier B, DeConde A, Luong AU, et al.International consensus statement on allergy and rhinology: rhinosinusitis 2021. Int Forum Allergy Rhinol. 2021;11(3):213–739. [PubMed: 33236525]
32. Gevaert P, Van Bruaene N, Cattaert T, Van Steen K, Van Zele T, Acke F, et al.Mepolizumab, a humanized anti-IL-5 mAb, as a treatment option for severe nasal polyposis. J Allergy Clin Immunol. 2011;128(5):989–95e1–8. [PubMed: 21958585]
33. Tuttle KL, Buchheit KM, Laidlaw TM, Cahill KN. A retrospective analysis of mepolizumab in subjects with aspirin-exacerbated respiratory disease. J Allergy Clin Immunol Pract. 2018;6(3):1045–7. [PubMed: 29501519]
34. Martin H, Barrett NA, Laidlaw T. Mepolizumab does not prevent all aspirin-induced reactions in patients with aspirin-exacerbated respiratory disease: A case series. J Allergy Clin Immunol Pract. 2021;9(3):1384–5. [PubMed: 32956852]

35. Laidlaw TM, Prussin C, Panettieri RA, Lee S, Ferguson BJ, Adappa ND, et al.Dexpramipexole depletes blood and tissue eosinophils in nasal polyps with no change in polyp size. Laryngoscope. 2019;129(2):E61–E6. [PubMed: 30284267]
36. Eid RC, Wudneh E, Zahid S, Cahill K, Jerschow E. Poor control of asthma symptoms with interleukin-5 inhibitors in four patients with aspirin-exacerbated respiratory disease. Ann Allergy Asthma Immunol. 2020;124(1):102–4. [PubMed: 31605753]
37. Laidlaw TM, Mullol J, Fan C, Zhang D, Amin N, Khan A, et al.Dupilumab improves nasal polyp burden and asthma control in patients with CRSwNP and AERD. J Allergy Clin Immunol Pract. 2019;7(7):2462–5e1. [PubMed: 30954643]
38. Bachert C, Han JK, Desrosiers M, Hellings PW, Amin N, Lee SE, et al.Efficacy and safety of dupilumab in patients with severe chronic rhinosinusitis with nasal polyps (LIBERTY NP SINUS-24 and LIBERTY NP SINUS-52): results from two multicentre, randomised, double-blind, placebo-controlled, parallel-group phase 3 trials. Lancet. 2019;394(10209):1638–50. [PubMed: 31543428]
39. Tokunaga T, Sakashita M, Haruna T, Asaka D, Takeno S, Ikeda H, et al.Novel scoring system and algorithm for classifying chronic rhinosinusitis: the JESREC Study. Allergy. 2015;70(8):995–1003. [PubMed: 25945591]
40. Stevens WW, Staudacher AG, Hulse KE, Poposki JA, Kato A, Carter RG, et al.Studies of the Role of Basophils in Aspirin Exacerbated Respiratory Disease Pathogenesis. J Allergy Clin Immunol. 2021.
41. Takahashi T, Kato A, Berdnikovs S, Stevens WW, Suh LA, Norton JE, et al.Microparticles in nasal lavage fluids in chronic rhinosinusitis: Potential biomarkers for diagnosis of aspirin-exacerbated respiratory disease. J Allergy Clin Immunol. 2017;140(3):720–9. [PubMed: 28238741]
42. Martin HC, Derakhshan T, Dwyer DF. Insights into mast cell hyperplasia in AERD from transcriptional profiling of polyp mast cells. Ann Allergy Asthma Immunol. 2021;in press.
43. Steinke JW, Payne SC, Borish L. Eosinophils and Mast Cells in Aspirin-Exacerbated Respiratory Disease. Immunol Allergy Clin North Am. 2016;36(4):719–34. [PubMed: 27712766]
44. Dwyer DF, Ordovas-Montanes J, Allon SJ, Buchheit KM, Vukovic M, Derakhshan T, et al.Human airway mast cells proliferate and acquire distinct inflammation-driven phenotypes during type 2 inflammation. Sci Immunol. 2021;6(56).
45. Christie PE, Tagari P, Ford-Hutchinson AW, Charlesson S, Chee P, Arm JP, et al.Urinary leukotriene E4 concentrations increase after aspirin challenge in aspirin-sensitive asthmatic subjects. Am Rev Respir Dis. 1991;143:1025–9. [PubMed: 1850964]
46. Steinke JW, Bradley D, Arango P, Crouse CD, Frierson H, Kountakis SE, et al.Cysteinyl leukotriene expression in chronic hyperplastic sinusitis-nasal polyposis: importance to eosinophilia and asthma. J Allergy Clin Immunol. 2003;111(2):342–9. [PubMed: 12589355]
47. Cahill KN, Boyce JA. Aspirin-exacerbated respiratory disease: Mediators and mechanisms of a clinical disease. J Allergy Clin Immunol. 2017;139(3):764–6. [PubMed: 27771324]
48. Buchheit K, Hulse KE. Local immunoglobulin production in nasal tissues: A key to pathogenesis in CRSwNP and AERD. Ann Allergy Asthma Immunol. 2021;in press.
49. Van Zele T, Gevaert P, Watelet JB, Claeys G, Holtappels G, Claeys C, et al.Staphylococcus aureus colonization and IgE antibody formation to enterotoxins is increased in nasal polyposis. J Allergy Clin Immunol. 2004;114(4):981–3. [PubMed: 15480349]
50. Perez-Novo CA, Kowalski ML, Kuna P, Ptasinska A, Holtappels G, van Cauwenberge P, et al.Aspirin sensitivity and IgE antibodies to Staphylococcus aureus enterotoxins in nasal polyposis: studies on the relationship. Int Arch Allergy Immunol. 2004;133(3):255–60. [PubMed: 14976394]
51. Steinke JW, Negri J, Liu L, Payne SC, Borish L. Aspirin activation of eosinophils and mast cells: implications in the pathogenesis of aspirin-exacerbated respiratory disease. J Immunol. 2014;193(1):41–7. [PubMed: 24890720]
52. Pal K, Ramsden M, Shim YM, Borish L, Payne SC, Steinke JW. Suppression of aspirin-mediated eosinophil activation by prostaglandin E2: Relevance to aspirin and nonsteroidal anti-inflammatory drug hypersensitivity. Ann Allergy Asthma Immunol. 2019;123(5):503–6. [PubMed: 31513909]

53. Paruchuri S, Jiang Y, Feng C, Francis SA, Plutzky J, Boyce JA. Leukotriene E4 activates peroxisome proliferator-activated receptor gamma and induces prostaglandin D2 generation by human mast cells. J Biol Chem. 2008;283(24):16477–87. [PubMed: 18411276]
54. Austen KF, Maekawa A, Kanaoka Y, Boyce JA. The leukotriene E4 puzzle: finding the missing pieces and revealing the pathobiologic implications. J Allergy Clin Immunol. 2009;124(3):406–14; quiz 15–6. [PubMed: 19647860]
55. Maekawa A, Kanaoka Y, Xing W, Austen KF. Functional recognition of a distinct receptor preferential for leukotriene E4 in mice lacking the cysteinyl leukotriene 1 and 2 receptors. Proc Natl Acad Sci U S A. 2008;105(43):16695–700. [PubMed: 18931305]
56. Ying S, Meng Q, Scadding G, Parikh A, Corrigan CJ, Lee TH. Aspirin-sensitive rhinosinusitis is associated with reduced E-prostanoid 2 receptor expression on nasal mucosal inflammatory cells. J Allergy Clin Immunol. 2006;117(2):312–8. [PubMed: 16461132]
57. Kay LJ, Yeo WW, Peachell PT. Prostaglandin E2 activates EP2 receptors to inhibit human lung mast cell degranulation. Br J Pharmacol. 2006;147(7):707–13. [PubMed: 16432506]
58. Sestini P, Armetti L, Gambaro G, Pieroni MG, Refini RM, Sala A, et al.Inhaled PgE2 prevents aspirin-induced bronchoconstriction and urinary LTE4 excretion in aspirin-sensitive asthma. American J Respiratory Critical Care Medicine. 1996;153:572–5.
59. Allakhverdi Z, Smith DE, Comeau MR, Delespesse G. Cutting edge: The ST2 ligand IL-33 potently activates and drives maturation of human mast cells. J Immunol. 2007;179(4):2051–4. [PubMed: 17675461]
60. Pan D, Buchheit KM, Samuchiwal SK, Liu T, Cirka H, Raff H, 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(3):1047–57e8. [PubMed: 30017554]
61. Arm JP, O'Hickey SP, Spur BW, Lee TH. Airway responsiveness to histamine and leukotriene E4 in subjects with aspirin-induced asthma. Am Rev Respir Dis. 1989;140:148–53. [PubMed: 2546469]
62. Lang DM, Aronica MA, Maierson ES, Wang XF, Vasas DC, Hazen SL. Omalizumab can inhibit respiratory reaction during aspirin desensitization. Ann Allergy Asthma Immunol. 2018;121(1):98–104. [PubMed: 29777744]
63. 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(5):1585–7e4. [PubMed: 26559322]
64. Hayashi H, Fukutomi Y, Mitsui C, Kajiwara K, Watai K, Kamide Y, et al.Omalizumab for Aspirin Hypersensitivity and Leukotriene Overproduction in Aspirin-exacerbated Respiratory Disease. A Randomized Controlled Trial. Am J Respir Crit Care Med. 2020;201(12):1488–98. [PubMed: 32142372]
65. Buchheit KM, Dwyer DF, Ordovas-Montanes J, Katz HR, Lewis E, Vukovic M, et al.IL-5Ralpha marks nasal polyp IgG4- and IgE-expressing cells in aspirin-exacerbated respiratory disease. J Allergy Clin Immunol. 2020;145(6):1574–84. [PubMed: 32199912]
66. Cahill KN, Katz HR, Cui J, Lai J, Kazani S, Crosby-Thompson A, et al.KIT Inhibition by Imatinib in Patients with Severe Refractory Asthma. N Engl J Med. 2017;376(20):1911–20. [PubMed: 28514613]
67. Doherty TA, Broide DH. Airway innate lymphoid cells in the induction and regulation of allergy. Allergol Int. 2019;68(1):9–16. [PubMed: 30473412]
68. Eastman JJ, Cavagnero KJ, Deconde AS, Kim AS, Karta MR, Broide DH, 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(1):101–8e3. [PubMed: 28279492]
69. Walford HH, Lund SJ, Baum RE, White AA, Bergeron CM, Husseman J, et al.Increased ILC2s in the eosinophilic nasal polyp endotype are associated with corticosteroid responsiveness. Clinical immunology. 2014;155(1):126–35. [PubMed: 25236785]
70. Miljkovic D, Bassiouni A, Cooksley C, Ou J, Hauben E, Wormald PJ, et al.Association between group 2 innate lymphoid cells enrichment, nasal polyps and allergy in chronic rhinosinusitis. Allergy. 2014;69(9):1154–61. [PubMed: 24924975]

71. Poposki JA, Klingler AI, Tan BK, Soroosh P, Banie H, Lewis G, et al.Group 2 innate lymphoid cells are elevated and activated in chronic rhinosinusitis with nasal polyps. Immun Inflamm Dis. 2017.

72. van der Ploeg EK, Golebski K, van Nimwegen M, Fergusson JR, Heesters BA, Martinez-Gonzalez I, et al.Steroid-resistant human inflammatory ILC2s are marked by CD45RO and elevated in type 2 respiratory diseases. Sci Immunol. 2021;6(55).

73. Doherty TA. At the bench: understanding group 2 innate lymphoid cells in disease. J Leukoc Biol. 2015;97(3):455–67. [PubMed: 25473099]

74. Smith SG, Chen R, Kjarsgaard M, Huang C, Oliveria JP, O'Byrne PM, et al.Increased numbers of activated group 2 innate lymphoid cells in the airways of patients with severe asthma and persistent airway eosinophilia. J Allergy Clin Immunol. 2016;137(1):75–86e8. [PubMed: 26194544]

75. Liu S, Verma M, Michalec L, Liu W, Sripada A, Rollins D, et al.Steroid resistance of airway type 2 innate lymphoid cells from patients with severe asthma: The role of thymic stromal lymphopoietin. J Allergy Clin Immunol. 2018;141(1):257–68.e6. [PubMed: 28433687]

76. Doherty TA, Broide DH. Lipid regulation of group 2 innate lymphoid cell function: Moving beyond epithelial cytokines. J Allergy Clin Immunol. 2018;141(5):1587–9. [PubMed: 29522852]

77. Doherty TA, Khorram N, Lund S, Mehta AK, Croft M, Broide DH. Lung type 2 innate lymphoid cells express cysteinyl leukotriene receptor 1, which regulates TH2 cytokine production. J Allergy Clin Immunol. 2013;132(1):205–13. [PubMed: 23688412]

78. Xue L, Salimi M, Panse I, Mjosberg JM, McKenzie AN, Spits H, 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(4):1184–94. [PubMed: 24388011]

79. Moro K, Yamada T, Tanabe M, Takeuchi T, Ikawa T, Kawamoto H, et al.Innate production of T(H)2 cytokines by adipose tissue-associated c-Kit(+)Sca-1(+) lymphoid cells. Nature. 2010;463(7280):540–4. [PubMed: 20023630]

80. Lund SJ, Portillo A, Cavagnero K, Baum RE, Naji LH, Badrani JH, et al.Leukotriene C4 Potentiates IL-33-Induced Group 2 Innate Lymphoid Cell Activation and Lung Inflammation. J Immunol. 2017.

81. Salimi M, Stoger L, Liu W, Go S, Pavord I, Klenerman P, et al.Cysteinyl leukotriene E4 activates human group 2 innate lymphoid cells and enhances the effect of prostaglandin D2 and epithelial cytokines. J Allergy Clin Immunol. 2017.

82. Mita H, Higashi N, Taniguchi M, Higashi A, Akiyama K. Increase in urinary leukotriene B4 glucuronide concentration in patients with aspirin-intolerant asthma after intravenous aspirin challenge. Clin Exp Allergy. 2004;34(8):1262–9. [PubMed: 15298568]

83. Liu T, Barrett NA, Kanaoka Y, Yoshimoto E, Garofalo D, Cirka H, et al.Type 2 Cysteinyl Leukotriene Receptors Drive IL-33-Dependent Type 2 Immunopathology and Aspirin Sensitivity. J Immunol. 2018;200(3):915–27. [PubMed: 29282304]

84. Fajt ML, Gelhaus SL, Freeman B, Uvalle CE, Trudeau JB, Holguin F, et al.Prostaglandin D(2) pathway upregulation: relation to asthma severity, control, and TH2 inflammation. J Allergy Clin Immunol. 2013;131(6):1504–12. [PubMed: 23506843]

85. Chang JE, Doherty TA, Baum R, Broide D. Prostaglandin D2 regulates human type 2 innate lymphoid cell chemotaxis. J Allergy Clin Immunol. 2014;133(3):899–901e3. [PubMed: 24210841]

86. Maric J, Ravindran A, Mazzurana L, Van Acker A, Rao A, Kokkinou E, et al.Cytokine-induced endogenous production of prostaglandin D2 is essential for human group 2 innate lymphoid cell activation. J Allergy Clin Immunol. 2019;143(6):2202–14.e5. [PubMed: 30578872]

87. Maric J, Ravindran A, Mazzurana L, Bjorklund AK, Van Acker A, Rao A, et al.Prostaglandin E2 suppresses human group 2 innate lymphoid cell function. J Allergy Clin Immunol. 2018;141(5):1761–73e6. [PubMed: 29217133]

88. Zhou W, Toki S, Zhang J, Goleniewksa K, Newcomb DC, Cephus JY, et al.Prostaglandin I2 Signaling and Inhibition of Group 2 Innate Lymphoid Cell Responses. Am J Respir Crit Care Med. 2016;193(1):31–42. [PubMed: 26378386]

89. Roca-Ferrer J, Garcia-Garcia FJ, Pereda J, Perez-Gonzalez M, Pujols L, Alobid I, et al.Reduced expression of COXs and production of prostaglandin E(2) in patients with nasal polyps with

or without aspirin-intolerant asthma. J Allergy Clin Immunol. 2011;128(1):66–72.e1. [PubMed: 21397936]

90. Cahill KN, Raby BA, Zhou X, Guo F, Thibault D, Baccarelli A, et al.Impaired E Prostanoid2 Expression and Resistance to Prostaglandin E2 in Nasal Polyp Fibroblasts from Subjects with Aspirin-Exacerbated Respiratory Disease. Am J Respir Cell Mol Biol. 2016;54(1):34–40. [PubMed: 26051534]
91. Laidlaw TM, Cutler AJ, Kidder MS, Liu T, Cardet JC, Chhay H, et al.Prostaglandin E2 resistance in granulocytes from patients with aspirin-exacerbated respiratory disease. J Allergy Clin Immunol. 2014;133(6):1692–701e3. [PubMed: 24486071]
92. 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(42):16987–92. [PubMed: 24085850]
93. Mjosberg JM, Trifari S, Crellin NK, Peters CP, van Drunen CM, Piet B, et al.Human IL-25-and IL-33-responsive type 2 innate lymphoid cells are defined by expression of CRTH2 and CD161. Nat Immunol. 2011;12(11):1055–62. [PubMed: 21909091]
94. Mjosberg J, Bernink J, Golebski K, Karrich JJ, Peters CP, Blom B, et al.The transcription factor GATA3 is essential for the function of human type 2 innate lymphoid cells. Immunity. 2012;37(4):649–59. [PubMed: 23063330]
95. 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(8):3537–45. [PubMed: 26342029]
96. 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(5):1566–76e5. [PubMed: 26691435]
97. Lee JU, Chang HS, Lee HJ, Bae DJ, Son JH, Park JS, et al.Association of interleukin-25 levels with development of aspirin induced respiratory diseases. Respir Med. 2017;123:71–8. [PubMed: 28137499]
98. Bankova LG, Dwyer DF, Yoshimoto E, Ualiyeva S, McGinty JW, Raff H, et al.The cysteinyl leukotriene 3 receptor regulates expansion of IL-25-producing airway brush cells leading to type 2 inflammation. Sci Immunol. 2018;3(28).
99. Karta MR, Rosenthal PS, Beppu A, Vuong CY, Miller M, Das S, et al.beta2 integrins rather than beta1 integrins mediate Alternaria-induced group 2 innate lymphoid cell trafficking to the lung. J Allergy Clin Immunol. 2017.
100. Puttur F, Denney L, Gregory LG, Vuononvirta J, Oliver R, Entwistle LJ, et al.Pulmonary environmental cues drive group 2 innate lymphoid cell dynamics in mice and humans. Sci Immunol. 2019;4(36).
101. Wojno ED, Monticelli LA, Tran SV, Alenghat T, Osborne LC, Thome JJ, et al.The prostaglandin D(2) receptor CRTH2 regulates accumulation of group 2 innate lymphoid cells in the inflamed lung. Mucosal immunology. 2015;8(6):1313–23. [PubMed: 25850654]
102. Moriyama S, Brestoff JR, Flamar AL, Moeller JB, Klose CSN, Rankin LC, et al.beta2-adrenergic receptor-mediated negative regulation of group 2 innate lymphoid cell responses. Science. 2018;359(6379):1056–61. [PubMed: 29496881]
103. Krishnamoorthy N, Burkett PR, Dalli J, Abdulnour RE, Colas R, Ramon S, et al.Cutting edge: maresin-1 engages regulatory T cells to limit type 2 innate lymphoid cell activation and promote resolution of lung inflammation. J Immunol. 2015;194(3):863–7. [PubMed: 25539814]
104. Schneider TR, Johns CB, Palumbo ML, Murphy KC, Cahill KN, Laidlaw TM. Dietary Fatty Acid Modification for the Treatment of Aspirin-Exacerbated Respiratory Disease: A Prospective Pilot Trial. J Allergy Clin Immunol Pract. 2018;6(3):825–31. [PubMed: 29133219]
105. Corren J, Parnes JR, Wang L, Mo M, Roseti SL, Griffiths JM, et al.Tezepelumab in Adults with Uncontrolled Asthma. N Engl J Med. 2017;377(10):936–46. [PubMed: 28877011]
106. Krug N, Hohlfeld JM, Kirsten AM, Kornmann O, Beeh KM, Kappeler D, et al.Allergen-induced asthmatic responses modified by a GATA3-specific DNAzyme. N Engl J Med. 2015;372(21):1987–95. [PubMed: 25981191]

107. Castro M, Corren J, Pavord ID, Maspero J, Wenzel S, Rabe KF, et al.Dupilumab Efficacy and Safety in Moderate-to-Severe Uncontrolled Asthma. N Engl J Med. 2018;378(26):2486–96. [PubMed: 29782217]

108. Wenzel S, Ford L, Pearlman D, Spector S, Sher L, Skobieranda F, et al.Dupilumab in persistent asthma with elevated eosinophil levels. N Engl J Med. 2013;368(26):2455–66. [PubMed: 23688323]

109. Ortega HG, Liu MC, Pavord ID, Brusselle GG, FitzGerald JM, Chetta A, et al.Mepolizumab treatment in patients with severe eosinophilic asthma. N Engl J Med. 2014;371(13):1198–207. [PubMed: 25199059]

110. Pavord ID, Korn S, Howarth P, Bleecker ER, Buhl R, Keene ON, et al.Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. Lancet. 2012;380(9842):651–9. [PubMed: 22901886]

111. Nair P, Wenzel S, Rabe KF, Bourdin A, Lugogo NL, Kuna P, et al.Oral Glucocorticoid-Sparing Effect of Benralizumab in Severe Asthma. N Engl J Med. 2017;376(25):2448–58. [PubMed: 28530840]

112. Kohanski MA, Workman AD, Patel NN, Hung LY, Shtraks JP, Chen B, et al.Solitary chemosensory cells are a primary epithelial source of IL-25 in patients with chronic rhinosinusitis with nasal polyps. J Allergy Clin Immunol. 2018;142(2):460–9e7. [PubMed: 29778504]

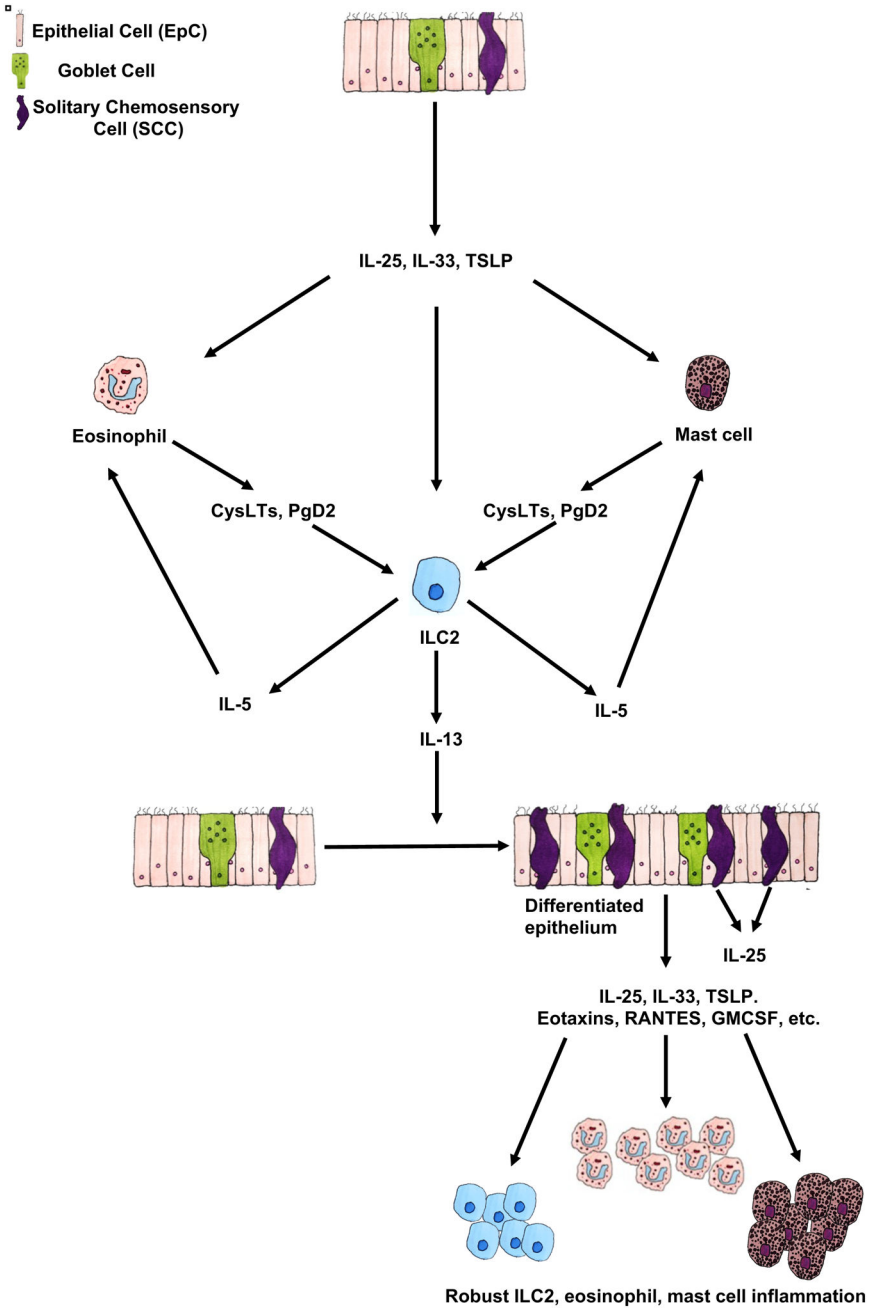

Figure:

Mediators produced epithelial cells in AERD and especially the cytokines IL-25, IL33, and TSLP recruit and activate innate immune cells including eosinophils, MCs, and ILC2s. Lipid mediators produced by eosinophils and MCs lead to the further activation of ILC2s. ILC2s through their secretion of IL-5 exacerbate eosinophilic inflammation. Numerous mediators released by all 3 of these cells but, in particular, ILC2-derived IL-13, lead to the further metaplastic transformation of the epithelium including the expansion of goblet cells and IL-25-producing solitary chemosensory cells. Together the epithelial and mucosal compartments of the innate immune system combine to produce a feed-

forward pro-inflammatory vicious circle with the continuously worsening inflammation that characterizes AERD.

Table I:

Innate Immune Cells in AERD

Cell Types	Select Mechanisms of Activation in AERD	Select Inflammatory products in AERD
Eosinophils	IL-5, IL-33	PGD_2, CysLTs
	Chemokines: eotaxins (CCL11/24/26), RANTES (CCL5)	EDN, ECP, MBP, EPX
		CLC/Galectin 10 IFN-γ L-plastin (fibrinogenesis)
MCs	IL-25, IL-33, TSLP	PGD_2, CysLTs
	Aspirin/NSAIDs IgE? CysLTs (LTE_4)	Tryptase Histamine
ILC2s	IL-25, IL-33, TSLP PGD2, CysLTs	IL-4, IL-5, IL-13

Abbreviations: CysLT – cysteinyl leukotriene, IL – interleukin, ECP – eosinophil cationic protein, EDN – eosinophil-derived neurotoxin, EPX – eosinophil peroxidase, MBP – major basic protein, NSAID – non-steroidal anti-inflammatory drug, RANTES – regulated upon activated, normal T cell expressed and presumably secreted, TSLP – thymic stromal lymphopoietin