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Role of group 2 innate lymphocytes in aspirin-exacerbated respiratory disease pathogenesis

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ABSTRACT

Aspirin-exacerbated respiratory disease (AERD) is characterized by chronic eosinophilic nasal polyps, asthma, and airway reactions upon cyclooxygenase (COX) 1 inhibition. AERD is present in up to 7% of adult patients with asthma and the underlying pathogenesis remains largely elusive but prostaglandin D_2, cysteinyl leukotrienes, mast cells, and type 2 cytokines are thought to contribute. A wealth of studies have recently implicated group 2 innate lymphoid cells (ILC2), a novel lineage-negative lymphocyte population that produces type 2 cytokines, in human allergic disease pathogenesis. Importantly, our recent work identified that ILC2s are recruited to the nasal mucosa of patients on AERD after COX-1 inhibitor administration. Here, we review the potential impact of ILC2s in the development and propagation of type 2 inflammation in AERD.

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Aspirin-exacerbated respiratory disease (AERD) is a type 2 immune-mediated respiratory disease associated with asthma and nasal polyposis, and is defined by hypersensitivity reactions from cyclooxygenase (COX) 1 inhibition. All nonspecific nonsteroidal inflammatory drugs are capable of triggering a reaction, in distinction to COX-2 specific inhibitors, which generally are safe in AERD. AERD is an endotype of chronic rhinosinusitis (CRS) with nasal polyposis (CRSwNP) as well as asthma.[1] As such, it is clear that a mechanistic understanding of AERD would inform a broader understanding of type 2 respiratory inflammation. Compared with patients who are aspirin tolerant and with similar diagnoses, AERD patients have more severe asthma and sinus disease.

It is evident that the pathophysiology of AERD steers this disorder toward more aggressive inflammatory consequences. What is unclear is whether the inflammation in AERD is just an increase in the magnitude of "ordinary" type 2 inflammation, similar to what is seen in many patients with asthma and most patients with CRSwNP in U.S. and European populations, or whether unique inflammatory components separate AERD from other inflammatory airway disorders. The likely possibility is that overlapping features of both conventional allergic inflammation and unique aspects are present in AERD.

Innate lymphoid cells (ILC) are recently identified immune cells of lymphoid origin.[2] These cells share some functions with T-helper (Th) cells, yet the lack of canonical T-cell receptors prevents antigenic specificity. ILCs that reside at mucosal surfaces augment immune activation through rapid and abundant cytokine production. Based on the cytokine output and transcriptional control elements, ILCs can be classified into type 1, type 2, and type 3, which correspond with Th1, Th2, and Th17/22 subtypes, respectively.[2] Group 2 ILCs (ILC2) are capable of producing interleukin (IL) 4, IL-5, IL-9, and IL-13 after stimulation by cytokines IL-25, IL-33, or thymic stromal lymphopoietin (TSLP) as well as lipid mediators prostaglandin D_2 (PGD_2) and cysteinyl leukotrienes (CysLTs).[3] IL-33, TSLP, and IL-25 are primarily produced by the epithelium in response to mucosal injury. Importantly, many environmental insults can trigger ILC2 responses, including viruses and allergens.

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The underlying cause of AERD is unknown, but several lines of evidence point toward an environmental triggering mechanism. Patients with AERD are three times more likely to have had early life second-hand smoke exposure.[4] AERD develops in most patients in the fourth decade of life, and approximately half of the patients described a viral upper respiratory infection at the onset of their illness.[5] Although genetic polymorphisms associated with AERD have been described, these are diverse, and no unifying genetic background seems to confer risk of AERD. Thus, it is likely that, in patients with a background of genetic risk, environmental cues are primarily responsible for disease initiation. Importantly, ILC2s are situated at mucosal surfaces and are responsible for transduction of inflammatory stimuli into activation signals for a more organized type 2 immune response and thus are ideal culprits to be initiating and propagating inflammatory signaling in AERD. A proposed diagram of how ILC2s might contribute to AERD pathogenesis is shown in Fig. 1.

Clinical Aspects of AERD

Significant heterogeneity exists within asthma; much recent work has been done on proper clinical phenotyping and immune characterization of patients with asthma. Phenotyping predicts treatment response because asthma associated with eosinophilia responds to anti–IL-5 based therapy, whereas patients with allergic asthma are more likely to respond to anti–immunoglobulin E (IgE) therapy.[6] Among patients with asthma and patients with sinus disease, the presence of AERD is strongly associated with severity.[7] Patients with AERD are much more likely to have polyp recurrence within 6 months after surgery and to have a much higher burden of surgery when compared with aspirin-tolerant sinus disease.[8]

Similarly, patients with asthma and with AERD are more likely to have been intubated for asthma and to have more severe airflow obstruction. In patients who were clinically phenotyped with severe asthma, the group contained larger numbers of patients with AERD, with approximately twice the rate of AERD than that seen in the general asthma community.[9–11] AERD is present in ~7% of all patients with asthma and a similar number in patients with chronic sinusitis.[12] In patients with severe asthma, AERD is overrepresented, with 15% having AERD, and, in patients with both severe asthma and nasal polyposis, rates of AERD might be as high as 30–40%.[11,13]

The use of aspirin as a therapy (after desensitization) has been well described, and most recommendations include commence this treatment after a debulking polypectomy in patients with recalcitrant disease.[14] Aspirin therapy, usually at a dose of 325 mg twice a day up to 650 mg twice a day has been shown to delay polyp recurrence, to significantly improve symptoms, and to decrease the need for systemic corticosteroids.[15,16] Other treatments include leukotriene modifier drugs, aggressive sinus rinses, and topical corticosteroids.[17] For

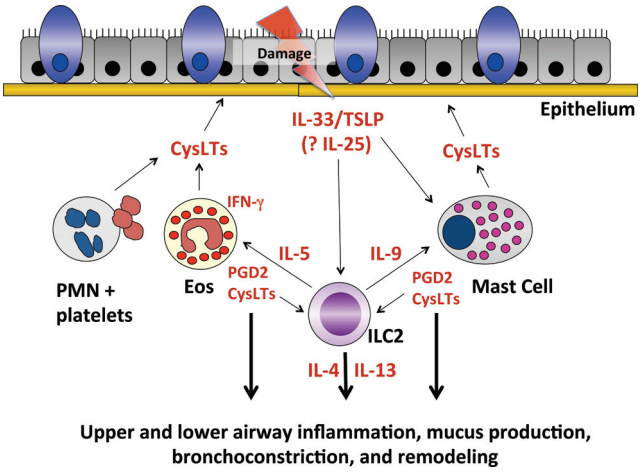

Figure 1. *Proposed role of group 2 innate lymphoid cells (ILC2) in aspirin-exacerbated respiratory disease (AERD) pathogenesis. Mast cells, eosinophils, and neutrophils (polymorphonuclear leukocytes, PMN) with adherent platelets produce ample cysteinyl leukotrienes (CysLT) in AERD. CysLTs and epithelial damage can then induce epithelial interleukin (IL) 25, IL-33, and thymic stromal lymphopoietin release that then directly activates ILC2s and mast cells. CysLTs and prostaglandin D_2 (PGD_2) from activated mast cells and eosinophils subsequently induce ILC2 IL-4, IL-5, and IL-13 production. ILC2 IL-5 propagates tissue eosinophilia, whereas IL-4 and IL-13 in concert with CysLTs and PGD_2 promote upper and lower airway inflammation, mucus production, bronchoconstriction, and tissue remodeling.*

patients with uncontrolled asthma, anti–IL-5 or anti-IgE treatments might also be an option.

Tissue Eosinophilia in AERD

AERD is invariably associated with nasal polyposis, and, although CRS without nasal polyposis is often mixed or type 1 inflammation, nasal polyposis is usually associated with eosinophilic polyp involvement. Interestingly, in the United States and in European countries, most nasal polyps are eosinophilic, whereas, in China, where nasal polyposis is typically noneosinophilic, AERD is extremely rare.[18,19] When compared with aspirin-tolerant polyps, AERD polyps contain twice as many eosinophils.[20] Similarly, bronchial biopsy specimens of subjects with AERD exhibited eosinophilia which is elevated when compared with patients with non-AERD asthma and increased eosinophiilic cationic protein (ECP) levels confirmed heightened activation of those eosinophils.[21]

Several unique characteristics are observed regarding eosinophils in AERD. Specifically, although IL-5, IL-3, and granulocyte-macrophage colony-stimulating factor (GM-CSF) are most commonly associated with expansion, recruitment, and terminal eosinophil differentiation, interferon (IFN) γ has also been detected in AERD tissue. Steinke *et al.*[22] and Steinke and Borish[23] demonstrated an IFN-γ level much higher in AERD polyps than in non-AERD polyps. In these studies, IFN-γ was being produced from the eosinophils themselves and acted in synergy with IL-5 to promote eosinophil survival. Subsequently, Stevens *et al.*[24] did not observe a strong IFN-γ signature in a survey of cytokines seen in AERD and sinus disease.

AERD is associated with a modest peripheral eosinophilia. During aspirin challenges, when the respiratory reaction occurs, the circulating peripheral eosinophils completely disappear.[25] Given the unleashing of CysLTs, PGD_2, and other potent type 2 mediators, it is likely that the peripheral eosinophils are trafficking to the site of inflammation (upper and lower airway) and out of the periphery.

PGD_2 in AERD

PGD_2, until recently, has been associated exclusively with mast cell production. Having now been observed to be produced directly from eosinophils, its role should be more carefully examined in AERD, in which both cell types associated with PGD_2 production are dominant (eosinophils and mast cells).[26] In work from Fajt *et al.*,[27] an elevated PGD_2 axis is associated with severe asthma. Given the recognition of AERD as an asthma phenotype associated with severe disease, it should not be a surprise to find evidence for PGD_2 in the pathophysiology of AERD.

Cahill *et al.*[28] described a dominant role of PGD_2 in an AERD phenotype associated with severe gastrointestinal and cutaneous reactions to aspirin. Specifically, the suppression of PGD_2 by aspirin was incomplete at threshold doses that cause aspirin reactions.[28] Although their report identified a unique subphenotype of AERD, it is applicable to the importance of PGD_2 in AERD in general. This observation lends weight to the hypothesis that the therapeutic benefit in AERD might be, in part, related to pharmacologic inhibition of COX-1 and subsequent modulation of the PGD_2 signal.

Leukotrienes in AERD

One of the early mechanistic insights into AERD was the observation that leukotriene E_4 (LTE_4) is significantly elevated at baseline in AERD patients (sixfold higher), with further elevation after the aspirin-induced reaction.[29] Other components of the leukotriene pathway are upregulated in AERD, including leukotriene C_4 synthase (LTC_4S) in bronchial biopsy specimens as well as 5-lipoxygenase (5-LO) and LTC_4S in nasal mucosa.[21] There are at least four receptors involved in leukotriene C_4 (LTC_4), leukotriene D_4 (LTD_4) and LTE_4 signaling, including $CysLT_1$, $CysLT_2$, $P2Y_{12}$, and GPR99 receptors. $CysLT_1$ and $CysLT_2$ receptors have well-described functions in mediating the effects of LTC_4 and LTD_4 (including, *e.g.*, bronchoconstriction, eosinophil influx, and mucus production). LTE_4, the stable terminal leukotriene, has little effect on $CysLT_1$ and $CysLT_2$. Thus, the potent bronchoconstrictor effect of LTE_4 must be mediated through actions of an additional receptor. $P2Y_{12}$ and GPR99 receptors both recognize LTE_4 and might be important clinically in allergic inflammation.[30,31]

Type 2 inflammation in AERD

Type 2 inflammation specifically refers to an eosinophilic and mast cell–rich inflammatory process driven by typical allergic cytokines, yet it broadens the mechanisms to include nonantigen or T-cell independent processes. Type 2 inflammation is appropriate to describe AERD, a disease with intense eosinophilic and mast cell involvement yet in which specific IgE processes as directed by Th2 cells likely play a minor role. Type 2 innate inflammation is often orchestrated by the epithelium where various stimuli can lead to the production of TSLP, IL-33, and IL-25. Buchheit *et al.*[25] demonstrated that TSLP is responsible for increasing the synthesis of PGD_2 in mast cells. With COX-1 inhibition, one of the hallmarks of AERD reactions then becomes the release of PGD_2, with associated clinical effects.

Further work, by Liu *et al.*,[32] identified IL-33 as a central mediator that bridges epithelial injury with mast cell activation and eosinophil recruitment through the action of CysLTs.[32] Recently, plasma levels of IL-25 were found to be increased in patients with AERD compared with controls and correlated with reductions in forced expiratory volume in the first second (FEV1) after aspirin challenge.[33] These studies frame a new paradigm for AERD, in which initial epithelial injury and production of TSLP and/or IL-33, and possibly IL-25, directly affects mast cell and eosinophil recruitment and activation. It is interesting to speculate on the nature, severity, and duration of the initial inflammatory event that leads to the perpetually dysregulated AERD syndrome.

ILC2 Identification and Localization

Group ILC2s were initially reported in 2010 and are lineage-negative lymphocytes that produce high levels of IL-5 and IL-13.[3] Lineage negative implies that exclusion of other lymphocytes, including T, B, natural killer (NK), and natural killer T (NKT) cells, by using lineage-specific markers with flow cytometry is required to detect ILC2s. In addition to being lineage negative, human ILC2s express chemokine receptor homologous molecule expressed on Th2 lymphocytes (CRTH2, receptor for PGD2), IL-2R (CD25), IL-7R (CD127), and CysLT1 receptor. Human ILC2s have been detected in lung, bronchoalveolar lavage (BAL), nasal mucosa, nasal polyps, gastrointestinal tract, skin, and blood.[3] The widespread tissue distribution in humans allows for ILC2s to potentially contribute critically to type 2 responses in many organ systems and in a variety of diseases.

Regulation of ILC2 Activation

ILC2s produce large amounts of type 2 cytokines in response to epithelial cytokines IL-33, TSLP, and IL-25 as well as lipid mediators that include PGD_2 and CysLTs.[3] Initially, ILC2s were shown to be activated in mice by epithelial cytokines IL-25 and IL-33.[3] Although a rare population of lymphocytes, ILC2s produce massive amounts of IL-5 and IL-13 per cell (μg range for 50,000 cells) after stimulation *in vitro*.[34] Thus, despite low numbers, ILC2s likely contribute significantly to disease due to the impressive potency of Th2 cytokine production. Further, because they are not antigen specific, the possibility exists that the majority of the ILC2s present in a given tissue are activated by local stimulation. After the initial mouse studies, human ILC2s were reported to respond to TSLP in addition to IL-33 and thus bridges an important gap between the known elevation of TSLP in samples from patients with asthma and atopic dermatitis and the activation of ILC2s.[35] Prior to this, TSLP was largely thought to regulate adaptive $CD4^+$ Th2 cell responses through dendritic cell activation.[36]

Lipid mediators that include prostaglandins and leukotrienes are increased during type 2 inflammation and have pleiotropic effects on several inflammatory cell types as well as regulate bronchial hyperreactivity and tissue remodeling. The first study that linked lipid mediators and ILC2 responses showed that PGD_2 enhanced human blood ILC2 Th2 cytokine production, whereas lipoxin A4 prevented the PGD_2-mediated increase.[37] After this report, our group showed that mouse ILC2s highly express $CysLT_1$ receptor and rapidly produce high levels of IL-4, IL-5, and IL-13 when stimulated with LTD_4, which has the highest affinity for $CysLT_1$ R among the CysLTs.[38] More recently, CysLTs have been shown to activate human ILC2s and that both PGD_2 and CysLTs also promote chemotaxis of ILC2s.[39–41] Interestingly, prostaglandin I2 reduces ILC2 activation in mice and humans, which is supportive that lipid mediators contribute to complex regulation of ILC2s, depending on the cytokine milieu.[42] Overall, lipid mediators that are thought to be at the core of AERD pathogenesis are also potent ILC2 activators.

ILC2s in Asthma

Asthma and CRS are characteristic features of AERD. ILC2s have been shown to promote asthma features in mouse models and were recently detected in tissue samples from patients with CRS and patients with asthma.[3,43–49] The first study to identify ILC2s in the sputum of patients with asthma showed that sputum cytokine–producing ILC2s were elevated in patients with severe asthma, including those who were taking systemic corticosteroids.[44] The same group subsequently showed that airway allergen challenge in patients with mild asthma led to recruitment of ILC2s to the airway.[43] Another study demonstrated elevation of BAL $IL\text{-}13^+$ ILC2s in the airway of a heterogenous group of patients with asthma versus controls.[50]

A recent report indicated that human ILC2s become corticosteroid resistant in the presence TSLP, which is elevated in the BAL of patients with severe asthma compared with patients with nonsevere asthma.[51] Mouse models also support that TSLP renders ILC2s resistant to corticosteroid treatment.[52] Importantly, because TSLP may also contribute to AERD pathogenesis,[25] ILC2-driven responses that lead to tissue eosinophilia and airway hyperresponsiveness (AHR) in these patients may be refractory to corticosteroid treatment. Several groups also correlated changes in blood levels of ILC2s with the presence and severity of asthma, and suggest that blood ILC2s may be recruited from bone marrow to lung in asthma and might be a biomarker of disease.[53–55] Overall, ILC2s have emerged as key contributors to type 2 lung diseases, including asthma.

ILC2s in Allergic Rhinitis

Allergic rhinitis (AR) is largely considered an IgE-mediated nasal inflammatory disease, although ILC2 changes in the blood have been detected after allergen challenge and during pollen seasons.[56,57] Our initial studies to investigate peripheral blood ILC2s in AR found that nasal challenge with cat allergen in patients with cat-sensitized AR leads to increased ILC2s compared with diluent control challenge.[57] Supportive of ILC2 changes with allergen in AR, another study found that peripheral blood ILC2s were increased in patients with grass pollen AR during the pollen season compared with control patients.[56] Further, ILC2 levels were reduced by subcutaneous immunotherapy, which is also supported by another report.[58] However, a previous report found that a group of patients with AR at baseline had similar numbers of peripheral blood ILC2s in contrast to patients with allergic asthma who had higher levels of ILC2s.[55]

One possibility to explain this seeming discrepancy is that ILC2s in peripheral blood increase relative to baseline after allergen exposure, although baseline levels may not be significantly higher than the controls, especially outside of allergen season. Another possibility that was recently explored is whether different allergens have different effects on ILC2s in AR. Fan *et al*.[59] found that ILC2s were increased in peripheral blood in patients with house-dust mite AR compared with mugwort AR (ILC2s from mugwort AR were no different than healthy controls) and that *in vitro* ILC2 Th2 cytokine responses to IL-25 and IL-33 were increased in the house-dust mite AR group.[59] Mouse models are also supportive of these findings because responses to different allergens are known to result in different levels of IL-33 release and ILC2 activation.[60]

ILC2s in CRSwNPs

Nasal polyps are a primary feature of AERD and are a significant cause of morbidity for patients. Although the majority of patients with nasal polyps do not have AERD, the relationship between ILC2s and nasal polyposis may provide insight into AERD pathogenesis. Importantly, tissue from patients with CRS showed elevated levels of CysLTs, IL-33, TSLP, and PGD_2,[61–64] which could all activate ILC2s independently or in an additive or synergistic manner.[65] Multiple groups have demonstrated that ILC2s are enriched in nasal polyps compared with control tissue.[46,66–69]

Levels of ILC2s correlate positively with eosinophilic polyps (the endotype present in AERD) as well as blood eosinophils and symptom scores, and with or without the presence of allergy. The finding across multiple studies that ILC2s correlate with the eosinophilic polyp endotype strengthens ILC2s as prime candidates to drive polyp eosinophilia through IL-5 production. Functional assays from nasal polyp ILC2s are limited, but Mjosberg *et al*.[35] showed that polyp ILC2s and short-term ILC2 cell lines produce Th2 cytokines in response to IL-33 and TSLP, and that this was dependent on GATA binding protien 3 (GATA3), the master Th2 cytokine transcription factor. Overall, these studies strongly indicate that ILC2s may contribute to CRS and nasal polyp pathogenesis.

ILC2s in AERD

ILC2s have been strongly implicated in the pathogenesis of asthma and CRS. Patients with AERD have respiratory tissue eosinophilia with high levels of PGD_2, CysLTs, IL-33, IL-25, and TSLP, all of which could activate ILC2s.[25,28,32,70] Recently, our group was the first, to our knowledge, to report changes in levels of ILC2s in patients with AERD.[45] We measured nasal brushing and peripheral blood ILC2 levels at baseline and during and after COX-1 inhibitor reactions in patients with AERD. Concomitantly, symptom scores and urinary LTE_4 and PGD_2 metabolites were analyzed at the same time points.

We found that ILC2s were recruited to the nasal mucosa (increased in nose and reduced in blood) in AERD but not in two control patients, during COX-1 inhibitor reactions. Further, levels of nasal ILC2s correlated with symptom scores, and urinary LTE_4 and PGD_2 metabolites increased during reactions as expected. One potential mechanism for recruitment of ILC2s to the respiratory tract during reactions is through PGD_2 binding of CRTH2 on ILC2s. Because CRTH2 has become a target in the treatment of allergic diseases, whether ILC2 recruitment to the nose would be reduced after administration of a CRTH2 inhibitor is an interesting avenue for investigation. In addition, the effect of long-term aspirin desensitization on ILC2 levels might also provide insight into whether changes over time correlate with improvement in clinical status.

CONCLUSION

AERD is a complex disease with interplay between many inflammatory and structural cell types as well as cytokine and lipid mediators. The central clinical features of AERD are eosinophilic nasal polyposis, asthma, and respiratory reactions to COX-1 inhibitors. CysLTs and PGD_2 levels are elevated in samples from patients with AERD and have been known to promote many features present in the disease. Importantly, cytokines IL-33 and TSLP were recently found increased in AERD sinus tissue and may be promoted by CysLTs and epithelial damage. Further, IL-25 levels wer also shown to be elevated in the serum of patients with AERD.

ILC2s are a recently described lineage-negative lymphocyte population that rapidly and robustly produces Th2 cytokines after stimulation with many mediators, including IL-25, IL-33, TSLP, PGD_2, and CysLTs. We recently determined that ILC2s are recruited to the nasal mucosa during COX-1 inhibitor reactions in AERD and correlate with symptom scores.[45] These findings, along with a growing body of work on ILC2s in type 2 diseases, support a role for ILC2s in AERD. Future investigation is required to further phenotypically and functionally characterize ILC2s in these patients.

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