

Eosinophils and Mast Cells in Aspirin-Exacerbated Respiratory Disease



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KEYWORDS

- Eosinophil • Mast cell • Leukotriene • Cyclooxygenase • Prostaglandin
- Aspirin-exacerbated respiratory disease • Arachidonic acid

KEY POINTS

- Aspirin-exacerbated respiratory disease (AERD) is a disease of overproduction and hyper-responsiveness to lipid mediators.
- Mast cells and eosinophils are key drivers of AERD pathogenesis through production of proinflammatory mediators following aspirin stimulation.
- Because of their involvement, therapies that target mast cells and eosinophils may be useful in providing clinical benefit in AERD.

INTRODUCTION

In 1968, the term Samter triad was coined and was defined by the presence of nasal polyps, aspirin sensitivity, and asthma¹; however this disease is now referred to as aspirin-exacerbated respiratory disease (AERD) because asthma is not always present despite reactions to aspirin. AERD comprises as many as 7% of adult-onset asthmatics and up to 12% to 14% of adult asthmatics with severe asthma.^{2,3} This disorder is characterized by the unique intolerance to aspirin and other nonselective cyclooxygenase (COX) inhibitors.^{4–6} Other characteristics include hypereosinophilia, both in the circulation and in the tissue; a tendency to develop de novo in adulthood^{5,7,8}; and often an absence of identifiable atopy.^{5,7} Sinusitis is present in this disorder,

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the degree of which is often severe, and this is associated with complete or near-complete opacification of the sinus cavity.⁸ Although not a requirement, when asthma is present it often progresses in severity and is associated with aggressive airway remodeling.⁹

During aspirin reactions, many mediators are released, including cysteinyl leukotrienes (CysLTs), tryptase, eosinophil cationic protein (ECP), and prostaglandin D₂ (PGD₂), suggesting both mast cell and eosinophil activation.^{10–12} Recently, aspirin was shown to directly activate both of these cell types *ex vivo* potentiating mediator release.¹³ A predominant physiologic feature of AERD is the robust overproduction and overresponsiveness to CysLTs (inflammatory),^{11,14} while at the same time there is underproduction and underresponsiveness to the antiinflammatory lipid mediator PGE₂.^{15–17} These CysLTs have important proinflammatory and profibrotic effects that contribute to the asthma severity and to the extensive hyperplastic sinusitis and nasal polyposis.^{8,18,19} In addition, conversely, the downregulation of PGE₂ pathways reduces the constraints that would normally act to attenuate these proinflammatory pathways.²⁰ This article focuses on the role that eosinophils and mast cells play in contributing to these cardinal features of AERD.

EOSINOPHIL AND MAST CELL NUMBERS IN ASPIRIN-EXACERBATED RESPIRATORY DISEASE

Chronic sinusitis (CRS) is now recognized as a collection of disorders that result from inflammation of the sinuses and in many cases can be separated into different types based on the cellular infiltrate. One distinguishing feature in the nasal polyps that often form in association with chronic sinusitis is the presence or absence of eosinophils and among eosinophilic polyps a distinction can be made between AERD, allergic fungal sinusitis (AFS), and chronic hyperplastic eosinophilic sinusitis (CHES).^{21,22} Within the eosinophilic polyps, AERD has more than twice the number of eosinophils in the polyp tissue than AFS or CHES, implicating them as important cells in the disease process.²² Examination of bronchial biopsies from patients with AERD also revealed highly increased eosinophil numbers compared with aspirin-tolerant asthmatics and nonasthmatics.²³ These eosinophils were in an activated state, as shown by the presence of secretory ECP.²³

The authors have reported lower numbers of mast cells in nasal polyps from eosinophilic sinus disease compared with healthy tissue by both toluidine blue and chloroacetate (chymase) staining, and there was no difference between aspirin-tolerant and AERD groups.²² This finding contrasts with a previous report that found no difference in mast cell numbers in nasal polyps from AERD groups compared with allergic or nonallergic individuals via tryptase staining.²⁴ The differences in the results of these studies may reflect the use of different markers of mast cells (chymase vs tryptase) or the stratification of the groups, the study by Park and colleagues²⁴ not taking into account eosinophilic infiltration into the polyp tissue. Regardless, there do not seem to be more mast cells in nasal polyps in patients with AERD. However, this result may be erroneous, given the high expression of mast cell–derived mediators, and perhaps reflects the inability to stain for activated, granule-depleted mast cells (so-called phantom mast cells). Similarly, when the lungs have been examined, as with nasal polyposis (NP), smaller numbers of mast cells have been found in patients with AERD compared with nonasthmatic controls using immunohistochemistry to stain for tryptase-positive cells.²³ Another study examining the bronchial mucosa found increased numbers of tryptase-positive mast cells only in subjects

with non-aspirin-sensitive asthma: again, patients with AERD and healthy controls paradoxically had similar numbers.²⁵

DEVELOPMENT OF EOSINOPHILS AND MAST CELLS

Eosinophils develop from pluripotent hematopoietic stem cells in bone marrow that initially differentiate into eosinophil/basophil progenitors or colony-forming units (Eo/B CFU) (Fig. 1). Eo/B CFU are mononuclear cells that express CD34, CD35, and interleukin (IL)-5 receptors (CD125) that are capable of responding to appropriate cytokine signals, allowing differentiation into mature basophils and eosinophils.^{26,27} Eo/B CFU are increased in numbers in both the blood and bone marrow of allergic patients and further increases in their numbers are observed following allergen exposure.²⁷ These progenitors are also observed in nasal polyp tissue.²⁸ Several transcription factors, including GATA-1, PU.1, and C/EBP, are induced in response to appropriate cytokine signals and become involved in the development of the eosinophil lineage and eosinophil-associated genes.^{29–31} In vitro eosinophil differentiation experiments have shown that GATA-1 is the primary transcription factor responsible for this eosinophil lineage specification.³²

Three cytokines, IL-3, IL-5, and granulocyte-macrophage colony-stimulating factor (GM-CSF) play the most important roles in the regulation of eosinophil development (see Fig. 1). The function of IL-3 is the broadest because it leads to the expansion of a variety of cell types, including monocytes, megakaryocytes, erythrocytes, basophils, neutrophils, and eosinophils.²⁶ GM-CSF acts in a similar fashion, albeit with more mature precursor cells, inducing the formation of macrophages, neutrophils, and eosinophils.³³ IL-5 is the cytokine responsible for selective terminal differentiation of eosinophils³⁴ and stimulates the release of eosinophils from the bone marrow into

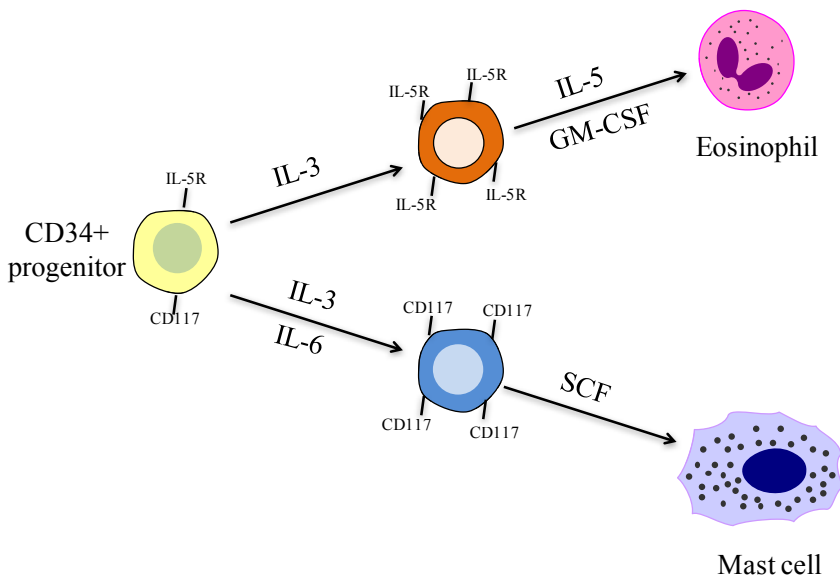


Fig. 1. Eosinophil and mast cell development from CD34 progenitor cells. Through the actions of interleukin (IL)-3, IL-5, and granulocyte-macrophage colony-stimulating factor (GM-CSF), CD34 progenitor cells mature into eosinophils. Mast cells develop following stimulation with IL-3, IL-6, and stem cell factor (SCF) from CD34 progenitor cells.

peripheral circulation.³⁵ GM-CSF, IL-3, and the chemokines CCL11, CCL24, and CCL26 (eotaxins) are also involved in eosinophil homeostasis and play an important role on arrival of the eosinophil at a tissue location. In addition, an interferon gamma (IFN- γ)-induced transcription factor ICSPB (IFN consensus sequence binding protein) can also drive the differentiation of eosinophils.³⁶ Because IFN- γ is routinely present in allergic inflammation and, in our studies, was particularly upregulated in AERD,³⁷ this led us to speculate on the role of IFN- γ being able to contribute to eosinophilia. Using an in vitro model with CD34⁺ hematopoietic progenitors, the authors showed the capacity of IFN- γ , acting in synergy with IL-5, to promote the survival and differentiation of mature bilobed, CCR3-expressing and Siglec-8-expressing eosinophils,³⁷ confirming prior studies³⁸ regarding the influence of this cytokine on eosinophil-mediated inflammation.

As with eosinophils, mast cells are derived from pluripotent hematopoietic CD34⁺ cells from the bone marrow,³⁹ but mast cells do not fully mature until they reach their final tissue destination, with the exception of mast cell leukemia. IL-3 and IL-6 increase early CD34⁺ progenitor cell numbers and begin the differentiation process; however, it is binding of stem cell factor (SCF) to its receptor c-Kit (CD117) that is the master growth and differentiation factor for human mast cells (see Fig. 1).⁴⁰ SCF is produced primarily by stromal cells⁴¹ and it can either be released as a soluble growth factor or expressed on the surface of these cells. It is the expression and binding of SCF at tissue sites that cause the CD34⁺ precursor cells to arrest and terminally differentiate into mast cells.

CYSTEINYL LEUKOTRIENE OVERPRODUCTION AND OVERRESPONSIVENESS IN ASPIRIN-EXACERBATED RESPIRATORY DISEASE

Arguably, the best-characterized molecules associated with AERD are the CysLTs. A unique characteristic of the disease is the overproduction of CysLTs in the resting state and a large surge in CysLT production in response to aspirin and other nonselective COX inhibitors that target COX-1.⁴² Included in this list are the nonselective nonsteroidal antiinflammatory drugs (NSAIDs) as well as other inhibitors of COX-1.^{43,44} The high CysLT levels in AERD reflect increased expression of the primary synthesis enzymes 5-lipoxygenase (5-LO) and, more importantly, leukotriene C₄ synthase (LTC₄S) (Fig. 2). Increased expression of these enzymes is observed in the lungs, sinuses, and nasal polyps of patients with AERD, with eosinophils and resident mast cells being the primary cells expressing the enzymes.^{15,18,23,45}

Not only do patients with AERD produce more CysLTs but they also show an increased sensitivity to CysLTs.⁴⁶ Initially, 2 CysLT receptors were identified and were distinguished from each other by their differing potency for the CysLTs: CysLT1 receptors primarily respond to LTD₄, whereas CysLT2 receptors respond equally to LTD₄ and LTC₄. Neither receptor responds well to LTE₄. Acting through CysLT1 and inhibited by the CysLT2 receptor, CysLTs induce mast cell proliferation through activation of c-kit and extracellular signal-regulated kinase.⁴⁷ In AERD sinus tissue, high levels of CysLT1 were found compared with healthy tissue, and following aspirin desensitization the CysLT1 levels returned to normal.⁴⁸ CysLT1 receptors are also prominently expressed on airway smooth muscle⁴⁹ and these receptors mediate a portion of the CysLT-induced bronchospasm associated with aspirin challenges or desensitizations,^{50–53} as shown by the ability of leukotriene receptor antagonists to attenuate much of the bronchospasm that occurs during these procedures.

Although these findings made it seem that CysLT1 was the only important leukotriene receptor in AERD, several observations suggested they were only partially

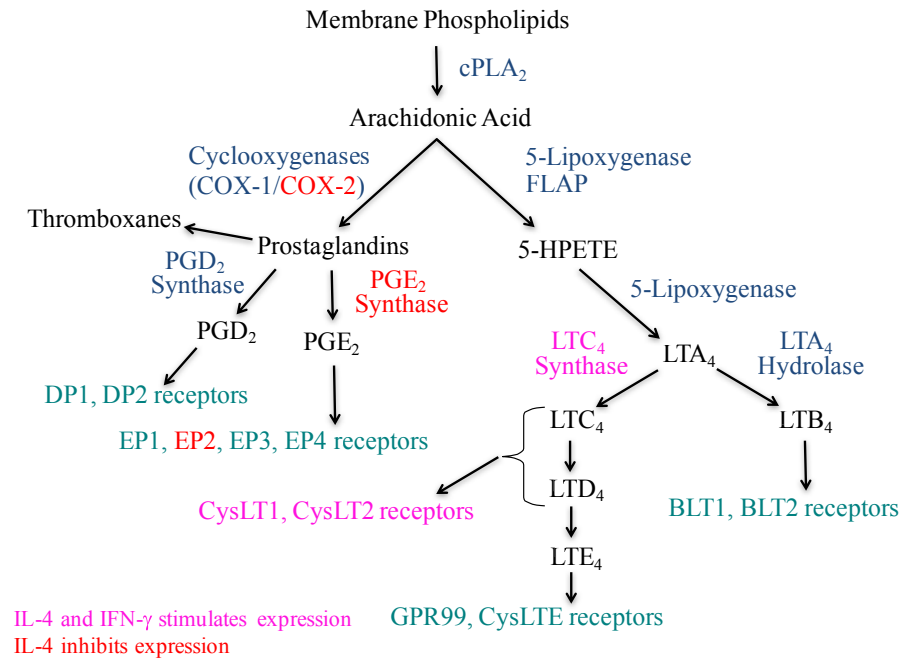


Fig. 2. Pathway depicting metabolites of arachidonic acid important in AERD. Following conversion to arachidonic acid by phospholipase A₂, further processing occurs via either the prostaglandin pathway mediated by COX-1/COX-2 or the leukotriene pathway mediated by 5-LO. Red lettering shows genes inhibited by IL-4 and pink lettering shows genes stimulated by IL-4 and IFN- γ .

involved in the pathogenesis of disease. The most abundant leukotriene found in the circulation and airway is LTE₄, with LTC₄ and LTD₄ being rapidly converted to LTE₄, thus limiting their duration of action in vivo. Inhalation of LTE₄ by asthmatic patients and patients with AERD potentiates airway hyperresponsiveness to subsequent challenges with histamine, the effect of which could be blocked with indomethacin.^{46,54,55} In the bronchial mucosa of asthmatics, inhalation of LTE₄, but not LTD₄, causes recruitment of eosinophils, basophils, and mast cells into the tissue.^{56,57} Mice in which both the CysLT1 and CysLT2 receptors have been deleted show enhanced skin swelling in response to intracutaneous LTE₄ compared with mice with these genes intact.⁵⁸ These studies led to the exploration for and ultimate identification of additional CysLT receptors that selectively respond to LTE₄ (GPR99 and P2Y12).^{58–61} The functional role of these LTE₄ receptors in AERD and the utility in targeting them as a therapeutic option are areas of active research, although diminished synthesis of CysLTs and, by extension, of LTE₄ could explain the superior efficacy of 5-lipoxygenase inhibitors in treating this disorder.⁶²

UNDERAPPRECIATED ROLE FOR PROSTAGLANDIN D₂ IN ASPIRIN-EXACERBATED RESPIRATORY DISEASE

PGD₂ and its metabolites have been found in blood and urine following aspirin challenge^{10,12,63} and the conventional thought is that it is primarily mast cell derived; however, reports show that eosinophils are also a source.^{64,65} Synthesis of PGD₂ is

regulated by hematopoietic PGD₂ synthase (hPGDS) (see Fig. 2) and when secreted it binds 2 receptors, CRTH2 (DP2) and DP1, that are expressed on numerous cell types. Activities of PGD₂ binding include stimulation of cell migration (including eosinophils and innate lymphoid type 2 cells), bronchoconstriction, vasodilation (flushing), and cellular activation and differentiation.^{66–69} A role for PGD₂ in the pathogenesis of AERD is supported by studies in chronic sinusitis. Expression of hPGDS has been observed in polyps, specifically in eosinophils.^{65,70,71} The degree of hPGDS expression correlated with eosinophil number and severity of disease. These studies did not examine patients with AERD but, given the high levels of eosinophilic infiltrate in AERD tissue, it is likely that hPGDS levels would have correlated as well. Recent work from our laboratory showed that, among CRS syndromes, in AERD the highest levels of hPGDS transcripts and proteins expression were observed and that eosinophils were the predominant cell type in which expression was localized.⁶⁵ As discussed articles in this issue, aspirin desensitization followed by high-dose aspirin therapy is often used to treat AERD; however, not all patients tolerate the desensitization protocol. It has recently been shown that patients who cannot be desensitized express higher basal levels of PGD₂ (and thromboxane) in their serum and urine.⁶³ During the desensitization procedure, these patients had a surge of PGD₂ release but not thromboxane, whereas those who were successfully desensitized had decreased thromboxane and unchanged PGD₂ levels.⁶³ The correlation between PGD₂ and eosinophil number in the polyp tissue was not assessed. Baseline PGD₂ level may serve as a marker to identify patients who will successfully undergo desensitization.

PROSTAGLANDIN E₂ AND PROSTAGLANDIN E₂ RECEPTOR DYSREGULATION IN ASPIRIN-EXACERBATED RESPIRATORY DISEASE

PGE₂ shows both proinflammatory and antiinflammatory functions, reflecting its ability to interact with 4 distinct receptors (EP1–EP4), each having various activating or inhibitory functions. However, it is the role of PGE₂ acting through antiinflammatory EP2 receptors to block eosinophil and mast cell degranulation that is central to the pathogenesis of AERD. Patients with AERD constitutively produce low levels of PGE₂,^{15,72} attenuating the antiinflammatory constraints provided by this lipid in this basal state. The further reduction of tissue PGE₂ concentrations by aspirin and other NSAIDs through COX-1 inhibition precipitates the activation of eosinophils and mast cells in AERD, as shown by the ability of inhaled PGE₂ to protect against these reactions.^{73,74} This sensitivity of patients with AERD to low tissue PGE₂ concentrations is amplified by their reduced expression of the antiinflammatory EP2 receptor.¹⁷ Serrapages and colleagues⁷⁵ showed that the ratio of EP2 to EP3 receptors on the surface of mast cells influences the activation potential of these cells when the high affinity immunoglobulin E receptor (FcεRI) is stimulated in a PGE₂-containing milieu. Through examination of various mast cell lines, the investigators found that patients with high levels of EP2 could suppress FcεRI activation in the presence of PGE₂, but when EP3 levels were high FcεRI activation of mast cells was enhanced. It is likely that the low EP2/EP3 ratio on mast cells and possibly eosinophils in AERD contributes to this disease because any PGE₂ that is available would preferentially signal through the EP3 receptor and activate these cells, thus contributing to the proinflammatory cascade.

Several studies have investigated the mechanism behind the reduced levels of PGE₂ in AERD and, perhaps not surprisingly, have correlated this with a decrease in the levels of the relevant upstream metabolic enzymes. The production of PGE₂ from arachidonic acid (see Fig. 2) involves the sequential synthesis of PGG₂/PGH₂ by the 2 COX enzymes (COX-1 and COX-2) followed by the synthesis of PGE₂ by

the microsomal PGE₂ synthases (mPGES-1, mPGES-2) and cytosolic PGE₂ synthase (cPGES). It is mPGES-1 that is most relevant to PGE₂ production in inflammatory disorders such as AERD because it is the enzyme primarily functionally coupled to COX-2.⁷⁶ COX-2 messenger RNA (mRNA) and protein expression are markedly diminished in AERD.^{15,16,77} Our studies have confirmed this diminished expression of COX-2.⁷⁸ We found no significant change in COX-1 and a trend toward diminished mPGES-1 expression and that this is driven in part by IL-4. Diminished COX-2 expression and the reduced capacity to synthesize PGE₂ contributes to the severity of inflammation observed in AERD and accentuates the sensitivity of these individuals to the further inhibition of PGE₂ synthesis associated with aspirin and other NSAIDs. With this shortage of COX-2, patients with AERD become dependent on COX-1 for the PGE₂ that is necessary to restrain mast cell and eosinophil activation. Thus, most patients with AERD tolerate selective COX-2 inhibitors,⁷⁹ supporting this concept regarding the unique importance of COX-1–derived PGE₂.

CYTOKINE EXPRESSION IN ASPIRIN-EXACERBATED RESPIRATORY DISEASE

Numerous studies have examined the cytokine milieu found in the tissue of eosinophilic sinusitis and AERD. Many of these studies have reported expression of a Th2-like immune profile (IL-4, IL-13, and IL-5), similar to other allergic diseases with eosinophilic infiltrate, although few have specifically focused on AERD.^{80–87} However, numerous observations suggest that, in contrast with patients with eosinophilic sinusitis who tolerate aspirin, AERD seems to have a mixed Th2-like and Th1-like cytokine milieu characterized by prominent expression of IFN- γ . The first study to suggest this examined patients with nonallergic sinusitis and showed enhanced IFN- γ expression in this cohort, a group in which AERD is likely to be overexpressed.⁸⁸ Since this initial report, high levels of IFN- γ in chronic sinusitis have been reported by other investigators, although patients with AERD were not specifically separated or recruited for the studies.⁸⁹ One study specifically addressed IFN- γ expression in AERD and found enhanced levels of IFN- γ in circulating CD8⁺ cells compared with aspirin-tolerant controls.⁹⁰ The concept that AERD reflects a mixed Th2-like and Th1-like cytokine profile was confirmed in our recent study in which NP tissue derived from patients with AERD was contrasted with tissue obtained from aspirin-tolerant and control subjects by the overexpression of IFN- γ mRNA transcripts and protein.³⁷ To our surprise, eosinophils themselves were the most important source for this cytokine, which is consistent with previous studies showing that IFN- γ can be expressed by eosinophils in substantial quantities.^{91–93} In contrast with our findings, a recent report did not find increased levels of IFN- γ protein in nasal polyps from patients with AERD; however this group did not perform flow cytometry, immunohistochemistry, or quantitative polymerase chain reaction to verify their results.⁸⁷

CYTOKINE DYSREGULATION OF LEUKOTRIENE C4 SYNTHASE AND CYSTEINYL LEUKOTRIENE RECEPTORS

Under noninflammatory conditions, mast cells express moderate levels of LTC₄S that can be increased greatly following stimulation by IL-4 (but not by IL-5 or IL-13).⁹⁴ It has also been observed that IFN- γ also has the capability of upregulating LTC₄S expression in umbilical cord–derived mast cell progenitors (J Boyce, personal communication, 2013). Although mast cells are capable of synthesizing CysLTs, previous studies²³ have shown that eosinophils are the more important cell type overexpressing LTC₄S in AERD. Examining a battery of cytokines (including IL-3, IL-4, IL-5, GM-CSF, IL-1, tumor necrosis factor alpha, and IFN- γ), the authors were unable to

show an ability of any of these cytokines to modulate LTC₄S expression on circulating eosinophils. This inability may be caused by their terminal differentiation state and short life span. The authors have also failed to show the ability of IL-4 to increase LTC₄S expression on eosinophils differentiated from progenitors in the presence of IL-3 and IL-5. However, when the progenitors were incubated with IFN- γ during the differentiation stage, a significant increase in LTC₄S expression was observed.³⁷ The increase in LTC₄S expression translated into increased capacity of these newly differentiated eosinophils to secrete CysLTs on activation by aspirin.¹³ Another mechanism of CysLT production involves the transcellular conversion of LTA₄ by adherent platelets expressing LTC₄S.⁹⁵ The frequencies of platelet-adherent eosinophils, neutrophils, and monocytes are markedly increased in the blood of patients with AERD. Any LTA₄ that is released into the extracellular space can be captured by the platelets and converted to CysLTs. It has been estimated that adherent platelets contribute up to 50% of the total LTC₄S activity in blood and thus would represent a significant source of the CysLTs found in AERD.⁹⁵

CysLT receptor expression is regulated by numerous cytokines, including IL-4 and IFN- γ but also IL-5 and IL-13. IL-4 increases expression of CysLT1 on mast cells^{96,97} and monocytes.⁹⁸ In our studies, IL-4 also increased the expression of both CysLT1 and CysLT2 on T and B lymphocytes and eosinophils.⁹⁹ We also showed robust upregulation of CysLT1 and CysLT2 receptors in response to IFN- γ on T cells and eosinophils.⁹⁹ In recent studies, examination of eosinophils derived from CD34⁺ progenitors has also shown the ability of IFN- γ to upregulate CysLT1 and CysLT2 receptor expression.³⁷ There have been no reports of cytokine modulation of other CysLT receptors. In summary, in the AERD cytokine environment, both mast cells and eosinophils are primed to produce and respond to the CysLTs that are produced during the disease process.

CYTOKINE DYSREGULATION OF PROSTAGLANDIN E₂ SYNTHESIS AND EP₂ RECEPTORS

Cytokine regulation of the PGE₂ synthesis pathway in AERD has not been thoroughly investigated. However, in other model systems, the influence of IL-4 on COX-2 expression has been reported. Inhibition of COX-2 expression by IL-4 was noted using peripheral blood monocytes, alveolar macrophages, and non-small cell lung cancer cells.^{100–102} The authors performed studies on nasal polyp-derived fibroblasts and mononuclear phagocytic cells. Monocytes were used as representative inflammatory cells but also because PGE₂ is their dominant prostaglandin product. Similar to other findings, significant inhibition of COX-2 and also mPGES-1 (but not COX-1) mRNA and protein expression was observed following stimulation with IL-4 on both the monocytes and nasal polyp-derived fibroblasts.⁷⁸ Inhibition of COX-2 and mPGES-1 synergizes to result in dramatically less stimulated PGE₂ secretion by monocytes.⁷⁸ IL-13 has been reported to have a similar effect on airway epithelial cells.¹⁰³ Thus, in addition to enhancing the CysLT pathways, IL-4 and IL-13 contribute to the AERD phenotype through inhibition of the PGE₂ pathway. The role of IFN- γ modulation of the prostaglandin pathway is unclear because its action seems to be cell-type specific. IFN- γ can induce COX-2 mRNA in most inflammatory cells,^{104,105} whereas it decreases COX-2 expression in placental¹⁰⁶ and intestinal epithelial cancer cells.¹⁰⁷ Actions of IFN- γ on other parts of the PGE₂ pathway have not been studied in detail.

ACTIVATION OF EOSINOPHILS AND MAST CELLS BY ASPIRIN

It was unknown in AERD how aspirin triggered the release of proinflammatory mediators. Although, as noted, inhibition of COX releases the protective constraints

provided by PGE₂, this alone does not explain the positive signaling driving cell activation. In a particularly robust murine model of AERD, aspirin sensitivity is induced by the knocking out of the mPGES-1 gene.¹⁰⁸ In this model, the positive (activating) signal is provided by allergic inflammation, a mechanism not likely to be relevant in AERD, at least in those patients with AERD who are not atopic. The authors speculated that aspirin and other NSAIDs had the inherent capacity to directly activate eosinophils and mast cells. When tested, both eosinophils and mast cells generated Ca⁺² fluxes following stimulation with water-soluble lysine aspirin (LysASA).¹³ Similar results were observed with eosinophil activation measured by eosinophil derived neurotoxin (EDN) release and eosinophil and mast cell secretion of PGD₂.^{13,65} When eosinophils from control, aspirin-tolerant patients, and patients with AERD were compared, no differences were observed in levels of mediator release. Our explanation as to why hypersensitivity reactions resulting from mediator release caused by aspirin/NSAIDs are not observed in these control cohorts reflects alterations in their PGE₂ sensitivity, specifically the decreased capacity to produce and respond to this antiinflammatory mediator observed in AERD. We speculate that the higher expression of PGE₂, as well as its antiinflammatory EP2 receptor, acts to prevent the acute reactions to aspirin/NSAIDs in controls and aspirin-tolerant asthmatics.^{20,73} An additional explanation for the absence of clinical symptoms in these control cohorts is that, when activated with aspirin, their circulating eosinophils produced very low levels of CysLTs,¹³ in contrast with the robust levels found in patients with AERD following aspirin ingestion.⁴² As mentioned earlier, AERD sinonasal and lung tissue is characterized by high numbers of eosinophilic hematopoietic progenitor (CD34⁺IL-5R α ⁺) cells.^{28,109} We therefore investigated whether eosinophils differentiated from progenitor cells in the presence of IFN- γ would recapitulate the sensitivity to aspirin shown by tissue eosinophils in vivo in AERD. After maturation with IFN- γ , the mature eosinophils showed increased gene expression for both LTC₄S and hPGDS.^{13,65} Consistent with the increase in LTC₄S gene expression, CysLT secretion was dramatically increased on LysASA activation.¹³ In addition to increased CysLT production, these IFN- γ matured eosinophils showed enhanced PGD₂ production when stimulated with LysASA.⁶⁵

SUMMARY: TOWARD A GENERALIZED MODEL FOR THE INDUCTION OF THE ASPIRIN-EXACERBATED RESPIRATORY DISEASE PHENOTYPE

Although it has been understood for many years that aspirin causes reactions and that AERD is a debilitating disease, the exact mechanisms driving AERD and how to treat it are still largely unknown. Our work and that of others have shown the importance of both eosinophils and mast cells as drivers of the disease leading to increased expression of proinflammatory mediators and reflecting the loss of protective PGE₂. The ultimate result is constitutive overproduction of and overresponsiveness to mediators by eosinophils and mast cells in the basal state in AERD, with the uncontrolled release of mediators when these cells are directly triggered by aspirin. The increased recognition of the cellular components and mechanisms of action in AERD provides an opportunity to develop alternative targeted therapeutic approaches designed to dampen the severe impacts of this disease.

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