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Prostaglandin E2 in NSAID-exacerbated respiratory disease: Protection against cysteinyl leukotrienes and group 2 innate lymphoid cells

Mark Rusznak, B.A.^a and R. Stokes Peebles Jr., M.D.^a

^aDivision of Allergy, Pulmonary and Critical Care Medicine, Department of Medicine, Vanderbilt University School of Medicine, Nashville, TN, USA

Structured Abstract

Purpose of Review: The purpose of this review is to describe the recent advances that have been made in understanding the protective role of PGE₂ in aspirin-exacerbated respiratory disease (AERD), known in Europe as non-steroidal anti-inflammatory drug (NSAID) exacerbated respiratory disease (N-ERD).

Recent Findings: Decreased PGE₂ signaling through the EP₂ receptor in patients with AERD leads to an increase in leukotriene synthesis and signaling. Leukotriene signaling can directly activate group 2 innate lymphoid cells (ILC2) and mast cells, but it also increases production IL-33 and TSLP. These cytokines drive Th2 inflammation in a suspected feed-forward mechanism in patients with AERD.

Summary: Recent discoveries concerning the role of PGE₂ in leukotriene synthesis and signaling in AERD, as well as downstream effects on ILC2 and mast cells, allow for a more comprehensive understanding of the pathogenesis of this disease. These discoveries also identify new paths of potential investigation and possible therapeutic targets for AERD.

Keywords

N-ERD; AERD; PGE₂; IL-33; TSLP; ILC2

Introduction: Aspirin-Exacerbated Respiratory Disease (AERD)

AERD, known in Europe as non-steroidal anti-inflammatory drug (NSAID) exacerbated respiratory disease (N-ERD),⁽¹⁾ is a syndrome characterized by asthma, rhinitis, nasal polyps, excess mucus production, and eosinophilic inflammation, all worsened by the ingestion of medications that inhibit cyclooxygenase (COX)-1. The disease was first documented as a triad of symptoms (nasal polyps, non-allergic asthma, and aspirin-sensitivity) by the French physician Ferdinand Widal in 1922.⁽²⁾ However, the condition

Address correspondence to: Stokes Peebles, M.D., Division of Allergy, Pulmonary and Critical Care Medicine, Vanderbilt University School of Medicine, T-1218 MCN, VUMC, 1161 21st Ave South, Nashville, TN 37232-2650, USA, Telephone: 615-343-3412; fax: 615-343-7448, stokes.peebles@vanderbilt.edu.

Conflicts of Interest

None

first received widespread attention when it was described by Beers and Samter in 1968,(3) and the three quintessential symptoms identified by Widal are now collectively referred to as “Samter’s triad.”(4) In addition to these symptoms, others may include sinus pain, cough, skin flushing and/or urticarial rash in response to aspirin ingestion. Approximately 75% of patients with AERD also report respiratory reactions when consuming alcoholic beverages.(5,6) The disease was identified in the context of aspirin sensitivity and named accordingly, but AERD confers intolerance to all COX-1, but not COX-2, inhibiting non-steroidal anti-inflammatory drugs (NSAIDs).(7,8) AERD generally develops during the fourth decade of life.(9,10) On average, the onset of AERD occurs 3 years earlier in women than in men, and women with AERD have 2.5 times the number of hospitalizations for asthma exacerbations compared to men with the condition. A recent meta-analysis of numerous AERD cohort studies estimates the prevalence of AERD to be 7% in the general population and 14% amongst individuals with severe asthma.(11) Compared to aspirin-tolerant asthmatics, individuals suffering from AERD are at a two-fold greater risk for having uncontrolled asthma, are 80% more likely to visit the emergency room because of asthma attacks, and are 60% more likely to be hospitalized for asthma.(12) Measuring a decrease in lung function after inhaled aspirin challenge remains the standard method of diagnosis for AERD. An increase in cysteinyl leukotrienes (CysLT) in the urine after inhaled aspirin challenge is another indicator of AERD, and concentrations of LTE₄, a CysLT, above 241pg/mg Cr in the urine after aspirin challenge identifies a patient as positive for AERD with 92% specificity. However, most commercial labs are not equipped to quantify CysLTs, so the diagnostic utility of the urine test is limited.(13) Many patients do not notice that their asthmatic symptoms are connected to NSAID use, so physicians often do not consider administering aspirin challenge.(14,15) As a result, AERD is under-diagnosed, and the true prevalence of the disease is likely higher. The central cause of AERD remained poorly understood until recently. In this review, we detail mechanisms underlying AERD pathogenesis. We outline the contributions of the CysLT pathway to AERD, and discuss how prostaglandin E₂ (PGE₂) signaling through the prostaglandin (PG) E₂ receptor EP₂ inhibits CysLT generation and restrains inflammation. We then discuss recent developments in our understanding of AERD and describe new pathways that contribute to this disease.

Pathogenesis of AERD: CysLTs and PGE₂

CysLTs are a principal driving force of AERD pathogenesis.(16) CysLTs, like prostaglandins, are down-stream metabolic products of arachidonic acid. If 5-lipoxygenase (5-LO) catalyzes arachidonic acid, it becomes the CysLT precursor 5-hydroperoxyeicosatetraenoic acid (5-HPETE), which can be metabolized to LTA₄ (Figure 1).(17)(18) LTA₄ may be metabolized to LTB₄ by the enzyme LTA₄ hydrolase.(14,18) Alternatively, LTA₄ can be catalyzed by LTC₄ synthase to react with glutathione to produce LTC₄ and its downstream metabolites LTD₄ and LTE₄. LTD₄ and LTE₄ act through multiple receptors and cell types to induce the canonical inflammatory phenotypes of asthma.(18) There are 3 CysLT receptors: CysLT₁R, CysLT₂R, and CysLT₃R. CysLT₃R was formerly known as GPR99.(19,20) LTC₄ and LTD₄ signal through CysLT₁R to induce smooth-muscle contraction.(21,22) Both human and guinea pig studies have implicated CysLT₂R signaling in driving bronchoconstriction.(23–25) LTE₄ signals through CysLT₁R and CysLT₃R, the

latter of which stimulates mucin release and submucosal swelling in the nasal mucosa of mice.(26) Leukocyte-adhering platelets, mast cells, eosinophils, and basophils are the primary contributors to LTC₄, LTD₄, and LTE₄ production.(27,28) CysLT₁R is expressed on mast cells, macrophages, and granulocytes, leading to an enhanced, multi-cellular inflammatory reaction in response to LTC₄, LTD₄, and LTE₄ synthesis and signaling.(29,30) Increases in CysLTs further enhance Th2 inflammation by directly activating group 2 innate lymphoid cells (ILC2) through CysLT₁R and by increasing the expression of other activating cytokine receptors such as thymic stromal lymphopoietin receptor (TSLPR) and the IL-33 receptor subunit suppression of tumorigenicity 2 (ST2).(31,32) These cells, their receptors, and their modes of activation will be discussed later.

One of the most important pieces of evidence that CysLTs are centrally involved in AERD is that LTE₄ levels increase directly in response to aspirin challenge in patients with AERD. The urine LTE₄ concentrations of subjects intolerant to NSAIDs were nearly six-fold greater than those of their non-NSAID sensitive asthmatic counterparts.(33) Sinonasal tissue samples of patients with AERD had significantly increased levels of 5-LO mRNA, LTC₄, LTD₄, and LTE₄ compared to healthy controls. 5-LO mRNA, LTC₄, LTD₄, and LTE₄ all increased in proportion to the severity of AERD in the test subjects.(34) An increase in the expression of enzymes critical for leukotriene synthesis, as well as an increase in leukotriene receptors on inflammatory cells, partially explain disease pathogenesis in AERD patients. Bronchial biopsies from NSAID sensitive and non-sensitive patients revealed that those with AERD have a nearly 18-fold increase in the number of cells that express LTC₄ synthase, correlating with baseline CysLT levels.(35,36) Nasal biopsy samples from AERD-affected and non-affected individuals revealed that patients with AERD had a nearly 5-fold increase in the number of cells expressing CysLT₁R in the airway, and the percentage of CD45⁺ leukocytes expressing this receptor was similarly 5-fold higher (25% vs. 5%) in AERD patients.(37) In discussing the contributions of leukotrienes to AERD, these pathways require regulatory mechanisms to keep them from exhibiting severe pathological effects. PGE₂ signaling emerged as the primary candidate responsible for keeping the CysLT pathway in check, and deficiencies in PGE₂ synthesis and signaling are major contributors to AERD pathogenesis.

COX1/COX2 catalysis of arachidonic acid results in the generation of the unstable product prostaglandin H₂ (PGH₂). PGH₂ has five preliminary down-stream conversion options depending on the tissue specific synthases that may be expressed by a cell. PGH₂ can be converted to PGD₂ by lipocalin-type PGD synthase or hematopoietic PGD synthase, PGI₂ by PGI synthase, thromboxane by thromboxane synthase, and PGF_{2α} by PGF synthase. Four PGE synthases (microsomal PGE synthase-1 [mPGES-1], microsomal PGE synthase-2 [mPGES-2], cytosolic PGE synthase [cPGES], and glutathione-s-transferase μ [GSTμ]) convert PGH₂ to PGE₂.(17,38) PGE₂ signals through 4 different receptors, E prostanoid receptor (EP) 1–4, with varying pro-inflammatory and anti-inflammatory functions, depending on the receptor through which PGE₂ signals.(17) In this regard, PGE₂ may have opposing functions within an individual cell depending of the level of expression of the individual EP receptors by that cell. PGE₂ attenuates the symptoms of asthma, and promotes these protective effects by signaling through the EP₂ receptor.(16) PGE₂ plays a critical role in relaxing smooth muscle cells through EP₂, allowing for a counteracting effect to

leukotriene-mediated bronchoconstriction.(39) Many different leukocytes also express EP₂ , and PGE₂/EP₂ regulates respiratory inflammation through a multitude of different pathways. (40) PGE₂ acts on CD4+ T helper cells to decrease their expression of pro-inflammatory cytokines, such as TNF- α , and promotes alveolar macrophages to produce the anti-inflammatory cytokine IL-10.(41,42) PGE₂ also limits eosinophil migration through EP₂ signaling, attenuating the eosinophilia phenotype common in asthma and allergic disease. (40,43) The PGE₂/EP₂ axis down-regulates degranulation of mast cells, leading to decreased histamine and tryptase levels.(44,45)Finally, and most importantly in regard to AERD, PGE₂ inhibits 5-LO function, preventing the synthesis of leukotrienes.(46) This inhibition occurs by PGE₂/EP₂ signaling increasing cAMP concentration within the target cell, preventing localization of 5-LO to the nuclear envelope, which is necessary for LTA₄ synthesis.(47) There is evidence to suggest that the PGE₂ inhibition of 5-LO activity might occur through an IL-10 dependent mechanism.(48)

Because of PGE₂'s protective effects in the setting of asthma, reduction of PGE₂ synthesis via aspirin could contribute significantly to the pathophysiology characteristic of AERD. The prevailing explanation for the difference in effect of NSAIDs between individuals with and without AERD is that COX 2 is unable to synthesize an adequate quantity of PGH₂ (and eventually PGE₂) upon inhibition of COX-1 in patients with AERD.(49) Nasal polyp biopsies from patients with AERD suggest that COX-2 expression is insufficient to produce a level of PGE₂ that inhibits 5-LO and generation of CysLTs.(50) The strongest evidence that PGE₂ signaling dysregulation drives AERD is that inhaled PGE₂ prevents respiratory reactions in patients with AERD who have been challenged with NSAIDs.(51) With PGE₂ inhalation, AERD subjects challenged with aspirin DL-lysine had no detectable increase in LTE₄ concentrations in the urine and no bronchoconstriction, indicated by no change in forced expiratory volume in 1 second (FEV₁). These results strongly suggest that PGE₂ has a protective role in AERD pathogenesis.(51)

It important to consider the possibilities of decreased PGE₂ production, decreased EP₂ receptor expression, or a combination of both contributing to the dysregulation of the PGE₂/EP₂ signaling axis in the pathogenesis of AERD. Recent evidence suggests that it is in fact a synergistic decrease in both PGE₂ levels and EP receptor density that contributes to the dysfunction of this protective pathway in AERD. There is a significant decrease in baseline PGE₂ levels in nasal tissue and peripheral blood cells in patients with AERD compared to healthy subjects, even without aspirin challenge.(14,16,34,52) It is not merely a deficiency of PGE₂ itself that contributes to AERD, but an inability of PGE₂ to signal through EP₂ because of EP₂'s restricted expression. There is a significant decrease in EP₂ signaling in fibroblasts from nasal polyps of AERD subjects compared to healthy controls. (53,54) Leukocytes in the nasal mucosa of subjects with AERD expressed EP₂ to a significantly reduced degree compared to leukocytes of those without NSAID sensitivity. (55) A lower percentage of neutrophils, mast cells, macrophages, and T cells in the bronchial mucosa of AERD subjects expressed EP₂ compared to unaffected individuals.(56) These data strongly support that defective PGE₂ signaling is at the center of AERD pathogenesis.

Recent advances: IL-33, TSLP and ILC2 are involved in AERD, and they are regulated by PGE₂

The relationship between CysLTs and PGE₂ has been investigated in the context of AERD for decades. However, more recent studies have described a role for IL-33 and thymic stromal lymphopoietin (TSLP) in AERD, and their conclusions have offered a more complete picture regarding the involvement of leukotrienes and how their immunopathogenic effects can be amplified. IL-33 is a major cytokine involved in Th2-like immune responses, including allergic airway diseases. IL-33 is an alarmin cytokine of the IL-1 family predominantly expressed by tissue cell types, including epithelial cells, fibroblasts, and endothelial cells, while its expression may be induced in immune cells such as macrophages, mast cells, and dendritic cells. In epithelial cells, IL-33 is released in response to cell necrosis, physical stress, or activation by protease-containing aeroallergens. (57) In mice, IL-33 is predominantly expressed in the lung by alveolar type II pneumocytes, while human lung IL-33 is expressed by bronchial epithelial cells. (57) By binding to its receptor ST2, IL-33 stimulates receptor-bearing cells to produce and secrete cytokines and growth factors that promote local and systemic immunity. ST2 is expressed on CD4⁺ Th2 cells, mast cells, eosinophils, and ILC2. ILC2 are an innate lymphoid subset that are similar to CD4⁺ Th2 lymphocytes, but they lack rearranged antigen-specific receptors so they are activated by soluble mediators such as IL-33, TSLP, and IL-25. (58,59) ILC2 secrete between 7 and 10-times the quantity of IL-5, a cytokine critical for eosinophil recruitment and activation, compared to CD4⁺ Th2 cells. ILC2 also release significant quantities of IL-13, which is a central mediator of airway responsiveness and mucous metaplasia. (60–62) In addition to IL-33, TSLP activates ILC2 and drives Th2 inflammation. TSLP signals through TSLPR, which is expressed on a variety of cell types, including T lymphocytes, B lymphocytes, monocytes, CD11c⁺ dendritic cells, and mast cells. (63) TSLP acts synergistically with IL-33 in the production of IL-5 and IL-13 by ILC2 in the lung. The unique importance of TSLP in lung ILC2 has recently been defined. While IL-33 activated ILC2 in the fat-associated lymphoid cluster of naïve mice, IL-33 alone was not able to induce IL-5 and IL-13 expression by mouse lung ILC2. Exogenous TSLP administration was required for the induction of large amounts of IL-5 and IL-13 from mouse lung ILC2. (60) The CysLT and ILC2 pathways likely interact with one another to drive the symptoms of AERD, and enhanced activation of ILC2 occurs in individuals with AERD. The hypothesized interplay between the CysLT and ILC2 pathway that we describe is highlighted in the right-hand portion of Figure 1.

ILC2 express CysLT₁R and CysLT₂R, and signaling through these receptors leads to an enhancement of ILC2 responses in mouse models. (52) LTC₄ signaling through both CysLT₁R and CysLT₂R significantly increased the proliferation and pro-inflammatory cytokine expression of IL-33-activated ILC2 in mouse airways. (64,65) These observations suggest that CysLTs directly stimulate ILC2, and as we previously discussed, CysLTs also act on mast cells to promote their degranulation. (29,30,66) We highlight that CysLTs act on ILC2 and mast cells directly because recent evidence suggests that there is an important secondary effect of leukotriene signaling that further enhances the inflammatory potential of ILC2 and mast cells in AERD. CysLTs stimulate mast cells and ILC2 through an IL-33/

TSLP-dependent mechanism to enhance immunopathogenic responses. In a mouse model, exogenous LTC₄ increased total expression of IL-33 in the lung, but only when CysLT₂R was expressed. House dust mite allergen significantly increased IL-33 expression specifically in type 2 pneumocytes in mice, but only when both LTC₄ synthase and CysLT₂R were expressed.(65) To our knowledge, CysLT dependent increases in IL-33 have only been investigated in type 2 pneumocytes. However, airway epithelial cells also express CysLT₂R and CysLT₃R.(26,67) CysLT signaling through CysLT₃R increased the expansion of brush cells secreting the pro-inflammatory cytokine IL-25, and CysLT₃R signaling increased mucin release from respiratory epithelial cells.(68,69) TSLP levels were significantly increased in the sputum of AERD patients after aspirin desensitization.(70) Six-month aspirin desensitization courses in patients with AERD lead to increased levels of LTC₄ in the sputum at both the 1 and 6 month marks. Although aspirin desensitization decreased PGD₂ and increased PGE₂, prolonged, elevated levels of CysLTs likely drove the increase of TSLP in the airway. These data suggest that there might be an increase in IL-33 and TSLP expression by epithelial cells in response to signaling through CysLT₂R or CysLT₃R, similar to type 2 pneumocytes. Further studies are necessary to identify the cell types in the respiratory tract that directly contribute to CysLT induced increases in IL-33 and TSLP. In addition to CysLTs, IL-13 may increase the expression of IL-33. Administration of recombinant IL-13 to alveolar epithelial cells *in vivo* increased IL-33 expression more than 8-fold.(71)

IL-33 and TSLP that are expressed due to CysLT signaling are released into the airways in response to cell necrosis, physical stress, or activation by protease-containing aeroallergens. (57) As previously discussed, IL-33 and TSLP signaling drive ILC2 proliferation and IL-5/IL-13 production. (58) IL-33 and TSLP also activate mast cells. IL-33 induced the production and release of PGD₂, TXB₂, and LTC₄ by human mast cells *in vitro*. (72) IL-33 was necessary for aspirin-induced mast cell degranulation in a mouse model of AERD. (73) Exogenous LTE₄ induced mast cell degranulation, but LTE₄ in the setting of IL-33 neutralization by either antibodies or anti-ST2 Fc fusion protein caused no significant release of histamine or the pro-inflammatory mediator prostaglandin D₂ (PGD₂) from mast cells. (73) TSLP also directly stimulated human mast cells *in vivo* to produce PGD₂. IL-33 acted synergistically with TSLP on mast cells *in vivo* to produce more PGD₂ compared to TSLP alone. (74) The interdependence of IL-33/TSLP, CysLT, and IL-13 pathway suggests a dangerous amplification mechanism that that can lead to enhanced inflammation and asthma in patients with AERD. The proposed mechanism is as follows. CysLT signaling is increased in patients with AERD, leading to an increase in IL-33 and TSLP. IL-33 and TSLP are released in episodes of inflammation, and they act synergistically with CysLTs to activate ILC2 and mast cells. ILC2 produce IL-5 and IL-13, and mast cells produce LTC₄, histamine, TXB₂, and PGD₂. IL-13 induces increased expression of IL-33 in epithelial cells. Histamine, PGD₂, and TXB₂ propagate the symptoms of asthma, and LTC₄ acts upstream to increase IL-33 and TSLP. IL-33 and TSLP continue to be expressed at high levels, and their release perpetuates a cyclic inflammatory response. This feed-forward mechanism has the potential for uncontrolled production of proinflammatory cytokines, leukotrienes, and histamine, leading to severe inflammation and bronchoconstriction.

We propose this synergistic pathway as an explanation for the severe respiratory symptoms that accompany AERD. There is substantial evidence to directly implicate IL-33 and TSLP in AERD pathogenesis. Nasal polyps isolated from patients diagnosed with AERD expressed significantly elevated levels of IL-33 compared to normal subjects. In a mouse model of AERD, deletion of the PGE synthase mPGES-1 increased baseline IL-33 in the lung, and concurrent deletion of LTC₄ synthase restored IL-33 to a normal level.(73) Concentrations of the cleaved, active form of TSLP were also significantly higher in the nasal polyps of patients with AERD compared to unaffected individuals.(74) ILC2 involvement in AERD is further evidenced by the recruitment of ILC2 to the nasal mucosa in AERD patients upon NSAID challenge, while no change in tissue or blood ILC2 numbers occurred upon administration of NSAIDs to non-AERD individuals.(75) These recent data strongly suggest that IL-33 and TSLP accentuated the leukotriene-mediated inflammatory response by acting synergistically with CysLTs to activate mast cells and ILC2, contributing persistent Th2 inflammation to the AERD phenotype.(76)

We present evidence that implicates ILC2 as an important contributing cell type in AERD pathogenesis. Recent experiments with human tonsillar and blood ILC2 have shown that PGE₂ decreased ILC2 expression of its principal transcription factor GATA-3. PGE₂ also down-regulated ILC2 production of IL-5 and IL-13, and PGE₂ decreased ILC2 proliferation in response to IL-33 and TSLP.(77) PGE₂'s inhibitory effect on ILC2 is dependent on signaling through EP₂ and EP₄, and PGE₂ signaling results in decreased expression of the IL-2 receptor α .(78) Because PGE₂ exhibits protective effects against the symptoms of AERD, PGE₂'s ability to attenuate ILC2 mediated immunopathology further supports the involvement of the IL-33/TSLP-ILC2 axis in AERD.

Conclusion

In summary, investigations surrounding AERD and its pathogenesis implicate the dysregulation of the CysLT pathway as a primary contributor to disease pathogenesis. Increases in CysLTs and leukotriene receptors on a range of cell types in AERD enhance the pathogenic nature of the CysLT pathway. PGE₂ signaling through the EP₂ receptor is a potent negative regulator of the CysLT pathway. Decreased PGE₂ synthesis from reduced COX-2 expression is exacerbated by COX-1 inhibiting NSAIDs in individuals with AERD. Because all COX-1 inhibitors, but not all NSAIDs, cause adverse reactions in people with AERD, we propose the name COX-One-inhibitor Exacerbated Respiratory Disease (COERD) as a more accurate alternative to AERD or N-ERD. Reduced PGE₂ synthesis in combination with decreased expression of EP₂ promotes CysLT synthesis and signaling in AERD patients. Recent evidence suggests that IL-33 and TSLP play a central role in driving AERD pathogenesis. CysLTs increase IL-33 and TSLP in the respiratory tract, and IL-33/TSLP act synergistically with CysLTs to activate ILC2 and mast cells. In AERD, ILC2 and mast cells produce mediators such as IL-13 to propagate Th2 inflammation and asthma, but mast cells also produce more LTC₄. IL-13 and LTC₄ increase upstream IL-33/TSLP expression. This positive feedback mechanism is likely a main driving force in AERD. However, PGE₂ can inhibit ILC2 function, making it a viable therapeutic option for AERD and other ILC2-mediated diseases.

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Key Points

- AERD is associated with increased CysLT production and expression of CysLT receptors.
- PGE₂ signaling through EP₂ negatively regulates CysLT production by inhibiting 5-LO function.
- CysLTs activate ILC2 and mast cells directly to propagate asthma, and PGE₂ inhibits these cells.
- CysLTs increase IL-33 and TSLP in the lung.
- IL-33 and TSLP act synergistically with CysLTs to activate ILC2 and mast cells.
- Activated mast cells release more leukotrienes that keep IL-33 and TSLP elevated, perpetuating inflammation.

Figure 1.

Known (left-section): The above figure describes the pathways of leukotriene and prostaglandin synthesis, and how these products affect inflammation and asthma. Pro-inflammatory signaling is represented with arrows, while protective, anti-inflammatory signaling is represented with perpendicular line-heads. The CysLTs LTC₄, LTD₄, and LTE₄ are expressed by neutrophil adhering platelets, mast cells, eosinophils, and basophils. CysLTs signal through the CysLT Receptors CysLT₁R, CysLT₂R, and CysLT₃R on T cells, macrophages, granulocytes, smooth-muscle cells and other cell types to propagate bronchoconstriction, mucin release, and inflammation (blue-dotted line). This encompasses the traditional understanding of CysLT-mediated asthma symptoms. PGE₂ (red-dotted line) protects against these symptoms by inhibiting 5-LO (responsible for CysLT synthesis) and signaling through the EP₂ receptor on T cells, macrophages, granulocytes, smooth-muscle cells and other pro-inflammatory cell types that are activated by CysLTs. **Newly proposed mechanisms (right section):** CysLTs cause increases in TSLP and IL-33 in the lung. TSLP and IL-33 are released from Type 2 alveolar cells and epithelial cells from cell stress, necrosis, or contact with aeroallergens. IL-33/TSLP act synergistically with CysLTs to activate group 2 innate lymphoid cells (ILC2) and mast cells. IL-33 signals through ST2, TSLP signals through TSLPR, and CysLTs signal through the CysLT receptors. This synergistic signaling causes ILC2 to release large quantities of IL-5 and IL-13. IL-13 then induces the increased expression of IL-33 in epithelial cells. CysLT and IL-33/TSLP signaling also causes mast cells to produce histamine, tryptase, PGD₂, and LTC₄. The LTC₄ released by mast cells (black-solid line) drives asthma as previously described, but LTC₄ also acts back upstream by increasing concentrations of IL-33 and TSLP in type 2

pneumocytes and likely epithelial cells. Increased quantities of IL-33 and TSLP drive a prolonged inflammatory response acting in synergy with CysLTs. PGE₂ inhibits ILC2 and mast cell activation, further suggesting PGE₂ dysregulation as a central cause of AERD.

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