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Review Article

Pathogenesis of NSAID-induced reactions in aspirin-exacerbated respiratory disease

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Abstract It is well-established that following ingestion of aspirin or any other inhibitor of cyclooxygenase-1, patients with Samter's disease, or aspirin-exacerbated respiratory disease (AERD) develop the sudden onset of worsening respiratory clinical symptoms, which usually involves nasal congestion, rhinorrhea, wheezing and bronchospasm. Gastrointestinal distress, nausea, a pruritic rash and angioedema can also occasionally develop. However, the underlying pathologic mechanism that drives these clinical reactions remains elusive. Pretreatment with medications that inhibit the leukotriene pathway decreases the severity of clinical reactions, which points to the involvement of cysteinyl leukotrienes (cysLTs) in the pathogenesis of these aspirin-induced reactions. Furthermore, studies of aspirin challenges in carefully-phenotyped patients with AERD have confirmed that both proinflammatory lipid mediators, predominantly cysLTs and prostaglandin (PG) D_2, and the influx of effector cells to the respiratory tissue, contribute to symptom development during aspirin-induced reactions. Mast cells, which have been identified as the major cellular source of cysLTs and PGD_2, are likely to be major participants in the acute reactions, and are an attractive target for future pharmacotherapies in AERD. Although several recent studies support the role of platelets as inflammatory effector cells and as a source of cysLT overproduction in AERD, it is not yet clear whether platelet activation plays a direct role in the development of the aspirin-induced reactions. To further our understanding of the pathogenesis of aspirin-induced reactions in AERD, and to broaden the pharmacotherapeutic options available to these patients, additional investigations with targeted clinical trials will be required.

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Introduction

Aspirin-exacerbated respiratory disease (AERD) is characterized by the triad of asthma, eosinophilic rhinosinusitis and nasal polyposis, and the onset of respiratory reactions induced by the ingestion of aspirin or any nonsteroidal antiinflammatory drugs (NSAIDs) that inhibit the cyclooxygenase (COX) 1 enzyme. The syndrome typically begins in young adulthood, with the onset severe nasal congestion, followed by progression to eosinophilic rhinosinusitis and recurrent nasal polyposis, and then the development of lower respiratory tract symptoms and eventually persistent asthma. The asthma is often severe, and patients with AERD tend to have lower baseline lung function than do those with aspirin-tolerant asthma, suggesting the presence of airway remodeling.[1] Lastly, if patients with AERD ingest any COX-1 inhibitor, an acute reaction develops within 1−3 h, which generally involves both upper and lower respiratory symptoms. Therefore, the disease encompasses two distinct disease phases: the chronic baseline respiratory tract inflammation that presents as asthma and recurrent nasal polyposis, and the acute hypersensitivity reactions triggered by COX-1 inhibitors. Although these respiratory reactions are the defining feature of the syndrome, the initial inflammatory respiratory disease process begins and continues independently of exposure to NSAIDs. However, the acute precipitation of worsening pathophysiology observed in the setting of an NSAID-induced respiratory reaction not only serves as the diagnostic gold standard for patients with AERD, but also offers insight into the cellular and biochemical abnormalities that underlie the syndrome.[2]

Both the baseline respiratory pathology and the clinical reactions to NSAIDs are accompanied by activation of effector cells, including mast cells and eosinophils, and by derangements in the metabolism of arachidonic acid, leading to the overproduction of both leukotrienes and prostaglandins (PGs). Unfortunately, neither the pathophysiology of the chronic underlying disease nor the mechanisms of the NSAID-induced reactions are completely understood, and future progress in this disease will require additional studies performed in carefully-phenotyped subjects with AERD.

Clinical features of NSAID-induced reactions

NSAID-induced reactions in patients with AERD tend to follow a very stereotyped clinical pattern. Classically, upper and/or lower respiratory symptoms will develop within 30−180 min after exposure to any inhibitor of COX-1 (e.g. aspirin, ibuprofen, naproxen, ketorolac). The most commonly noted respiratory symptoms include nasal congestion, rhinorrhea, sneezing, coughing, wheezing, and drop in lung function. These drug-induced symptoms are not immunoglobulin (Ig) E-dependent and therefore are more accurately classified as "hypersensitivity" reactions rather than "allergic" reactions. The respiratory reactions can also occasionally be triggered by higher doses of acetaminophen (≥1000 mg) which has mild COX-1 inhibitor properties,[3] but selective COX-2 inhibitors are generally considered to be safe for patients with AERD.[4,5]

There are several validated and clinically-useful NSAID-challenge protocols available in United States,[6,7] which use oral aspirin and/or intranasal instillation of ketorolac, with another protocol available in Europe and Asia[8] that uses intranasal lysine aspirin. In a subset of patients with AERD, in addition to the classical respiratory symptoms, NSAID exposure can also induce extra-pulmonary systemic symptoms involving both the skin and the gastrointestinal tract. These may present as flushing, macular rash, and/or pruritus, along with abdominal pain/cramping, and/or nausea and vomiting.[7,9] The route of NSAID challenge and the premedication regimen selected are key predictors of both respiratory symptom severity and rates of extra-pulmonary skin and gastrointestinal symptoms. In patients undergoing an oral aspirin challenge protocol who were not on a leukotriene modifying drug, 39% of them developed an aspirin-induced fall in FEV_1 of >20%, whereas only 18% of the patients who were on a leukotriene modifying drug (i.e. montelukast, zafirlukast, or zileuton) developed a fall in FEV1 of >20% during their aspirin-induced reaction.[10] Occasionally pretreatment with a leukotriene modifying drug may completely prevent reaction symptoms during aspirin challenge.[11] These effects of leukotriene modifying drugs support our current understanding of the inflammatory role of cysteinyl leukotrienes (cysLTs) in the pathogenesis of AERD and will be covered further below.

Altering the route of NSAID exposure from oral to intranasal decreases the severity of the respiratory and extra-pulmonary symptoms observed during the challenge. Because lysine aspirin, the more soluble form of aspirin, is not available in the United States, the standard intranasal protocol instead involves instillation of 4 doses of intranasal ketorolac before moving forward to complete the protocol with oral aspirin.[12] A study of patients desensitized to aspirin using this intranasal ketorolac protocol demonstrated that it is generally a safer way of achieving aspirin desensitization than a protocol using only oral aspirin administration. The intranasal ketorolac protocol decreased the severity of lower respiratory reactions and decreased the percentage of patients who developed extra-pulmonary reactions.[7] Intranasal lysine aspirin administration can similarly be used for aspirin challenge and also leads to less lower respiratory and extra-pulmonary symptoms than do oral aspirin protocols.[8] These intranasal challenge studies suggest that decreasing the systemic exposure to the COX-1 inhibitor decreases the development of systemic symptoms without compromising

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the ability to induce desensitization. Additionally, they suggest that there may be inflammatory contributions from effector cells and mediators that derive from both the local nasal tissues and the systemic circulation.

Pathophysiology of NSAID-induced reactions

The defining respiratory reactions in AERD are caused exclusively by drugs that inhibit the COX-1 isoenzyme. All COX-1 inhibitors trigger similar respiratory reactions, demonstrating that it is their pharmacologic action, and not an immunologic response, that provides their ability to induce reactions. Despite the somewhat stereotyped nature of the NSAID-induced reactions in patients with AERD, there is still significant patient-to-patient variation in the clinical presentation of these reactions, and the specific cellular and biochemical perturbations that cause the NSAID-induced reactions may vary from patient-to-patient. Indeed many complex and interconnected abnormalities have been reported in the cellular and mediator pathways that may contribute to AERD. No primary and universal pathologic mechanism has yet been identified for this disease, but much progress has recently been made in the field, and we are beginning to draw enough conclusions from which to eventually piece together the entire puzzle. We now know that specific lipid mediators, including cysLTs and prostaglandins, and several effector cells of the innate immune system, including mast cells and eosinophils, play key roles in the development of NSAID-induced reactions in AERD.

Lipid mediators

Leukotrienes

One of the first pathophysiologic findings noted in AERD was increased production of cysLTs, a class of potent inflammatory lipid mediators, derived from the metabolism of arachidonic acid.[13,14] Mast cells, eosinophils and platelet-adherent leukocytes, all of which are present at high concentrations in the respiratory tissue of patients with AERD, each have both functional 5-lipoxygenase and leukotriene C4 synthase enzymes, and therefore have the capacity to synthesize cysLTs. Using measurements of LTE_4, the stable end-metabolite of cysLTs, patients with AERD were found to have high baseline levels of cysLTs compared with healthy patients and aspirin-tolerant asthmatic (ATA) controls, which further increased in urine and nasal fluid during aspirin-induced reactions. Chronic levels of urinary LTE_4 are often 10-fold higher in AERD than in ATA patients, and they further increase during aspirin-induced reactions in AERD.[13] The magnitude of bronchoconstriction observed during provocative oral aspirin challenges is associated with the degree of baseline urinary LTE_4 elevation and the extent to which LTE_4 rises during reaction,[15] and higher baseline cysLT levels are associated with the development of both upper and lower respiratory symptoms during a reaction.[16] The cysLTs can induce edema, bronchoconstriction, and mucous secretion into the airways,[17–19] and LTE_4 induces recruitment of eosinophils to the respiratory tissues in asthmatic subjects.[20] Furthermore, drugs that either interfere with the synthesis of cysLTs, like the 5-lipoxygenase inhibitor zileuton, or block one of their receptors, like the CysLT1R antagonists, blunt the clinical and pathophysiological features of reactions to COX-1 inhibitors.[21,22] Therefore, cysLTs most certainly contribute to the development of NSAID-induced reactions in AERD, but neither the precise mechanism that triggers the overproduction of cysLTs, nor their cellular source(s) are known. There are several potential mechanisms for the overproduction of cysLTs in AERD, and current data supports a role for impairments in PGE_2 production[23] and the contributions of activated mast cells[21,24] and of platelet-leukocyte aggregates,[25] as detailed below.

Prostaglandins: prostaglandin D2, prostaglandin E2, and thromboxane A2

Prostaglandin D2 (PGD_2) is another inflammatory lipid mediator that is derived from the metabolism of arachidonic acid, and recent studies have suggested that it too is overproduced in AERD. Patients with AERD have been found to have high levels of PGD_2 or one of the metabolites of PGD_2 at baseline when compared with aspirin-tolerant controls.[26,27] These levels rise further during aspirin-induced reactions, with significant increases demonstrated at the onset of symptoms of clinical reaction in both the plasma[26] and the urine.[27,28] Additionally, baseline levels of urinary tetranor-PGD-M, one of the major urinary PGD_2 metabolites, correlate with the maximum fall in lung function, measured as a drop in FEV1, during aspirin-induced reactions and the rise in tetranor-PGD-M during reactions correlates with severity of clinical symptoms observed.[9] In fact, patients with AERD who are measured to have the highest PGD_2 levels during their aspirin-induced reactions are those who develop the most notable extra-respiratory symptoms, specifically rash and gastrointestinal distress, including abdominal pain and nausea, which can make it more difficult for patients to successfully complete their aspirin desensitization procedure.[9] These data suggest that PGD_2 plays a significant role in the clinical symptoms both at baseline and during aspirin-induced reactions in AERD. Considering the known biologic effects of PGD_2, there are several mechanisms by which PGD_2 may be responsible for components of the inflammatory state in AERD. First, the PGD_2 metabolite 9a,11b-PGF_2 is a potent bronchoconstrictor,[29] which is mediated through its signaling at the T prostanoid receptor (TP). PGD_2 is also a chemoattractant for several effector cell groups, including eosinophils, basophils, and innate lymphoid type 2 cells through the chemokine receptor homologous molecule expressed on Th2 lymphocytes (CRTH2).[30] The rise in PGD_2 production during aspirin-induced reactions correlates negatively with a fall in peripheral blood eosinophil levels, suggesting the chemotaxis of these $CRTH2^+$ cells out of the periphery and toward the respiratory tissue.[27] Finally, the positive correlation between nasal symptoms scores and PGD_2 levels may be due to the actions of PGD_2 at the DP1 receptor, which could cause acute swelling of the sinuses and airway, leading to the extreme nasal congestion that occurs during aspirin-induced reactions.

Though there is clearly mechanistic plausibility for a major role of PGD_2 in AERD, several unanswered questions remain. Neither the specific cellular source of PGD_2 is known, though it is assumed to be largely derived from activated mast cells, nor is the driver of the chronic overproduction of PGD_2 seen at baseline in some patients with

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AERD. Further, as PGD_2 is a COX-derived lipid, how is it that PGD_2 is being produced during aspirin-induced reactions, following pharmacologic inhibition of COX-1? We suspect that mast cells are the dominant cellular source of PGD_2, as it is the primary COX-derived product released from mast cells, and in addition to PGD_2, acute activation of mast cells leads to the release of tryptase, histamine and cysLTs, all of which are found at high levels in the respiratory fluids during aspirin-induced reactions.[21,24] Eosinophils, which are abundant in both the nasal polyps and the lung tissue in AERD, are another possible source of PGD_2. However, on a per-cell basis, eosinophils express much less transcript for*HPGDS*, the terminal PGD_2 synthase enzyme, than do mast cells.[27] As we now have the clinical availability of both anti-eosinophil agents and anti-CRTH2 agents, hopefully upcoming results of human studies using these drugs will provide us with more conclusive evidence for the role of PGD_2 in AERD.

It has long been surmised that the inhibition of COX-1 following aspirin ingestion may cause a decrease in COX-1-derived PGE_2, and that the loss of this anti-inflammatory prostaglandin could be a key mechanistic factor underlying aspirin-induced reactions in AERD. Several groups have shown abnormalities all along the PGE_2 production and signaling pathway, including specific deficiencies in the expression of COX-2, mPGES-1, and the EP_2 receptor in subjects with AERD.[31–36] These deficiencies could collectively reduce the ability of cells within the respiratory tissue to upregulate PGE_2 production during times of inflammation, making patients with AERD particularly sensitive to COX-1 inhibition. Two clinically-relevant findings support this hypothesis: (1) in 11 patients with AERD, PGE_2 levels in the bronchoalveolar lavage fluid fell significantly 15 min after bronchial aspirin challenge[37] and (2) pretreatment with inhaled PGE_2 prevented both the aspirin-induced rise in urinary LTE_4 and the aspirin-induced fall in FEV1 during aspirin challenge.[23] PGE_2 is known to negatively regulate the 5-lipoxygenaseenzyme[38] and an aspirin-induced fall in PGE_2 production in the local respiratory tissues could be a driving factor for the overproduction of cysLTs, which require metabolism through 5-lipoxynase. However, there are several reasons that during times of COX-1 inhibition, a simple "shunting" of COX-derived products to 5-lipoxygenase-derived products cannot be the underlying mechanism. First, such a shunting pathway would exist in all healthy patients as well, and no increase in cysLTs is noted in aspirin-tolerant patients following aspirin ingestion. Second, in cohort of patients with AERD, ingestion of aspirin did not cause a decrease in nasal PGE_2 level seven when their nasal cysLT levels did increase.[39]

Aspirin has been in medical use for over a century, and is well-known to have direct effects on other arachidonic acid metabolites as well, especially thromboxane (TX) A_2.[40] It is the anti-platelet effects that follow from aspirin-induced inhibition of TXA_2 that are thought to underlie the dramatic cardioprotective effects of low-dose aspirin. In addition to platelet activation, TXA_2 potently causes brochoconstriction,[41] mediating its effects through the TP receptor. As expected from the pharmacology, TXA_2 and its metabolites decrease during aspirin-induced reactions in most patients with AERD.[42] However, the subset of patients who demonstrate the most excessive PGD_2 overproduction during their reactions similarly demonstrate TXA_2 overproduction, as measured by an increase in the urinary metabolite11-dehydroTXB_2.[9] The TP receptor, which facilitates bronchoconstriction and through which both PGD_2 metabolites and TXA_2 can signal, is likely to play a role in the lower respiratory symptoms and fall in FEV1 that are so common during NSAID-induced respiratory reactions in AERD. Phase II clinical trials of a selective TP receptor antagonist in patients AERD[43] are ongoing and should better inform our understanding of the importance of this prostaglandin receptor signaling pathway.

A summary of the metabolism of arachidonic acid in respiratory tissues in patients with AERD is presented in Fig. 1.

Cells

The role of tissue mast cells, eosinophils, basophils and platelets have been the main focus of ongoing research in AERD, and evidence supports a role for each of these cells in mediator production and/or activation and migration to the respiratory tissue during NSAID-induced reactions.

Mast cells

Mast cells are long-lived effector cells in the that play a key role in respiratory tissue inflammation in AERD. In patients with AERD, aspirin-induced reactions cause an increase in nasal tryptase, histamine and cysLTs, and pretreatment with zileuton, a 5-lipoxygenase inhibitor, blocks both the clinical nasal symptoms and the increase in nasal tryptase and cysLTs. This demonstrates that mast cells are acutely activated during the reactions to NSAIDs, and that 5-lipoxygenase products (cysLTs) are important for the development of the clinical symptoms observed.[21] Tryptase and histamine can also increase systemically during aspirin reactions, and this tends to be most notable in patients with more severe reactions and with extra-pulmonary symptoms.[44] However, there are no differences in the numbers of mast cells within the nasal polyp tissue of patients with AERD[27] and there is no evidence that the mast cell activation measured during NSAID-induced reactions is IgE dependent. Therefore, it is unclear why mast cell activation occurs following NSAID ingestion in AERD and not in aspirin-tolerant healthy controls. One explanation is the impairment in PGE_2 production observed in subjects with AERD. PGE_2 serves as an inhibitor of 5-lipoxygenase, and therefore of mast cell activation[45] and the loss of this inhibition following the pharmacologic blockade of COX-1 may allow for unbraked mast cell activation.

Eosinophils/basophils

Chronic eosinophilic sinusitis and eosinophilic infiltration of the nasal polyp tissue is a hallmark of AERD. Tissue eosinophils likely drive much of the chronic inflammation in the respiratory tissue, and mild-to-moderate peripheral blood eosinophilia is also common in AERD.[27,46] Less is known about basophils in the disease, but during an aspirin-induced reaction, a migration of both eosinophils and basophils into the

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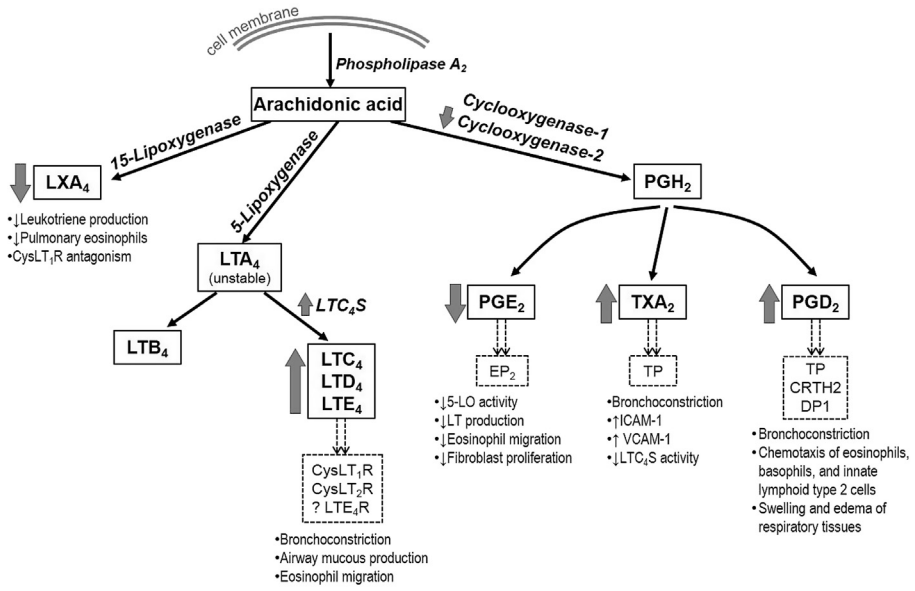

Fig. 1 Metabolism of arachidonic acid. The relevant pathways of arachidonic acid metabolism and consequences of lipid receptor signaling involved in the pathogenesis of AERD. Enzymes are in italics, receptors are in dashed boxes, and consequences of signaling through each receptor are in bulleted lists. Thick gray arrows demonstrate whether expression and function of each enzyme or product is increased or decreased in patients with AERD.

nose is observed,[47] and similarly into the bronchoalveolar lavage fluid following an inhaled aspirin challenge.[37] Correspondingly, a decrease of peripheral blood eosinophils within 1 h of the onset of reaction symptoms following aspirin challenge has been observed.[27,42] This migration of $CRTH2^+$ cells from the peripheral blood into the inflamed respiratory tissue, which occurs when PGD_2 levels are rising within the tissues, suggests that effector cells may be responding to a PGD_2 gradient produced from within the local tissue.[27]

Summary

It is generally accepted that the clinical symptoms invoked during NSAID-induced reactions in patients with AERD are due to both the acute release of proinflammatory lipid mediators, including cysLTs and PGD_2, and the rapid migration of effector cells, eosinophils and basophils and possibly others, into the respiratory tissues. Evidence also suggests that these lipid mediators are largely produced by mast cells. However, there are many remaining mysteries regarding the inciting trigger for the development of AERD, and regarding the underlying cause of the pathognomonic NSAID-induced reactions. Further translational research is required to fully understand the mechanisms of reaction, and we hope that understanding more about the pathogenesis of the COX-1 inhibitor-induced reactions will provide us with a better understanding of the disease overall.

Conflicts and interest

The author has no relevant disclosures to report.

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References

1. Szczeklik A, Nizankowska E, Duplaga M. Natural history of aspirin-induced asthma. AIANE investigators. European network on aspirin-induced asthma. *Eur Respir J*. 2000;16:432—436.
2. Stevenson DD, Szczeklik A. Clinical and pathologic perspectives on aspirin sensitivity and asthma. *J Allergy Clin Immunol*. 2006;118:773—786. quiz 787—788.
3. Szczeklik A, Gryglewski RJ, Czerniawska-Mysik G. Clinical patterns of hypersensitivity to nonsteroidal anti-inflammatory drugs and their pathogenesis. *J Allergy Clin Immunol*. 1977; 60:276—284.
4. Szczeklik A, Nizankowska E, Bochenek G, Nagraba K, Mejza F, Swierczynska M. Safety of a specific COX-2 inhibitor in aspirin-induced asthma. *Clin Exp Allergy*. 2001;31:219—225.
5. Dahlén B, Szczeklik A, Murray JJ. Celecoxib in patients with asthma and aspirin intolerance. The celecoxib in aspirin-intolerant asthma study group. *N Engl J Med*. 2001;344:142.
6. Berges-Gimeno MP, Simon RA, Stevenson DD. Early effects of aspirin desensitization treatment in asthmatic patients with aspirin-exacerbated respiratory disease. *Ann Allergy Asthma Immunol*. 2003;90:338—341.
7. Lee RU, White AA, Ding D, et al. Use of intranasal ketorolac and modified oral aspirin challenge for desensitization of aspirin-exacerbated respiratory disease. *Ann Allergy Asthma Immunol*. 2010;105:130—135.
8. Miller B, Mirakian R, Gane S, et al. Nasal lysine aspirin challenge in the diagnosis of aspirin — exacerbated respiratory disease: asthma and rhinitis. *Clin Exp Allergy*. 2013;43:874—880.

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9. Cahill KN, Bensko JC, Boyce JA, Laidlaw TM. Prostaglandin D_2: a dominant mediator of aspirin-exacerbated respiratory disease. *J Allergy Clin Immunol*. 2015;135:245–252.
10. White A, Ludington E, Mehra P, Stevenson DD, Simon RA. Effect of leukotriene modifier drugs on the safety of oral aspirin challenges. *Ann Allergy Asthma Immunol*. 2006;97:688–693.
11. Stevenson DD, Simon RA, Mathison DA, Christiansen SC. Montelukast is only partially effective in inhibiting aspirin responses in aspirin-sensitive asthmatics. *Ann Allergy Asthma Immunol*. 2000;85:477–482.
12. White A, Bigby T, Stevenson D. Intranasal ketorolac challenge for the diagnosis of aspirin-exacerbated respiratory disease. *Ann Allergy Asthma Immunol*. 2006;97:190–195.
13. Christie PE, Tagari P, Ford-Hutchinson AW, et al. Urinary leukotriene E4 concentrations increase after aspirin challenge in aspirin-sensitive asthmatic subjects. *Am Rev Respir Dis*. 1991;143:1025–1029.
14. Smith CM, Hawksworth RJ, Thien FC, Christie PE, Lee TH. Urinary leukotriene E4 in bronchial asthma. *Eur Respir J*. 1992; 5:693–699.
15. Daffern PJ, Muilenburg D, Hugli TE, Stevenson DD. Association of urinary leukotriene E4 excretion during aspirin challenges with severity of respiratory responses. *J Allergy Clin Immunol*. 1999;104:559–564.
16. Swierczynska M, Nizankowska-Mogilnicka E, Zarychta J, Gielicz A, Szczeklik A. Nasal versus bronchial and nasal response to oral aspirin challenge: clinical and biochemical differences between patients with aspirin-induced asthma/rhinitis. *J Allergy Clin Immunol*. 2003;112:995–1001.
17. Dahlén SE, Hedqvist P, Hammarström S, Samuelsson B. Leukotrienes are potent constrictors of human bronchi. *Nature*. 1980;288:484–486.
18. Dahlén SE, Hansson G, Hedqvist P, Björck T, Granström E, Dahlén B. Allergen challenge of lung tissue from asthmatics elicits bronchial contraction that correlates with the release of leukotrienes C4, D4, and E4. *Proc Natl Acad Sci U S A*. 1983;80: 1712–1716.
19. Dahlén SE, Björk J, Hedqvist P, et al. Leukotrienes promote plasma leakage and leukocyte adhesion in postcapillary venules: in vivo effects with relevance to the acute inflammatory response. *Proc Natl Acad Sci U S A*. 1981;78:3887–3891.
20. Gauvreau GM, Parameswaran KN, Watson RM, O'Byrne PM. Inhaled leukotriene E(4), but not leukotriene D(4), increased airway inflammatory cells in subjects with atopic asthma. *Am J Respir Crit Care Med*. 2001;164:1495–1500.
21. Fischer AR, Rosenberg MA, Lilly CM, et al. Direct evidence for a role of the mast cell in the nasal response to aspirin in aspirin-sensitive asthma. *J Allergy Clin Immunol*. 1994;94:1046–1056.
22. Dahlén SE, Malmström K, Nizankowska E, et al. Improvement of aspirin-intolerant asthma by montelukast, a leukotriene antagonist: a randomized, double-blind, placebo-controlled trial. *Am J Respir Crit Care Med*. 2002;165:9–14.
23. Sestini P, Armetti L, Gambaro G, et al. Inhaled PGE2 prevents aspirin-induced bronchoconstriction and urinary LTE4 excretion in aspirin-sensitive asthma. *Am J Respir Crit Care Med*. 1996;153:572–575.
24. Mita H, Endoh S, Kudoh M, et al. Possible involvement of mast-cell activation in aspirin provocation of aspirin-induced asthma. *Allergy*. 2001;56:1061–1067.
25. Laidlaw TM, Kidder MS, Bhattacharyya N, et al. Cysteinyl leukotriene overproduction in aspirin-exacerbated respiratory disease is driven by platelet-adherent leukocytes. *Blood*. 2012; 119:3790–3798.
26. Bochenek G, Nagraba K, Nizankowska E, Szczeklik A. A controlled study of 9alpha,11beta-PGF2 (a prostaglandin D2 metabolite) in plasma and urine of patients with bronchial asthma and healthy controls after aspirin challenge. *J Allergy Clin Immunol*. 2003;111:743–749.
27. Buchheit KM, Cahill KN, Katz HR, et al. Thymic stromal lymphopoietin controls prostaglandin D2 generation in patients with aspirin-exacerbated respiratory disease. *J Allergy Clin Immunol*. 2016;137:1566–1576.e5.
28. Higashi N, Mita H, Ono E, et al. Profile of eicosanoid generation in aspirin-intolerant asthma and anaphylaxis assessed by new biomarkers. *J Allergy Clin Immunol*. 2010;125:1084–1091.e6.
29. Beasley CR, Robinson C, Featherstone RL, et al. 9 alpha,11 beta-prostaglandin F2, a novel metabolite of prostaglandin D2 is a potent contractile agonist of human and Guinea pig airways. *J Clin Invest*. 1987;79:978–983.
30. Monneret G, Gravel S, Diamond M, Rokach J, Powell WS. Prostaglandin D2 is a potent chemoattractant for human eosinophils that acts via a novel DP receptor. *Blood*. 2001;98: 1942–1948.
31. Roca-Ferrer J, Garcia-Garcia FJ, Pereda J, 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;128:66–72.e1.
32. 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;117:312–318.
33. Corrigan CJ, Napoli RL, Meng Q, et al. Reduced expression of the prostaglandin E2 receptor E-prostanoid 2 on bronchial mucosal leukocytes in patients with aspirin-sensitive asthma. *J Allergy Clin Immunol*. 2012;129:1636–1646.
34. Adamusiak AM, Stasikowska-Kanicka O, Lewandowska-Polak A, et al. Expression of arachidonate metabolism enzymes and receptors in nasal polyps of aspirin-hypersensitive asthmatics. *Int Arch Allergy Immunol*. 2012;157:354–362.
35. Laidlaw TM, Cutler AJ, Kidder MS, et al. Prostaglandin E2 resistance in granulocytes from patients with aspirin-exacerbated respiratory disease. *J Allergy Clin Immunol*. 2014;133:1692–1701.e3.
36. Cahill KN, Raby BA, Zhou X, 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;54:34–40.
37. Szczeklik A, Sladek K, Dworski R, et al. Bronchial aspirin challenge causes specific eicosanoid response in aspirin-sensitive asthmatics. *Am J Respir Crit Care Med*. 1996;154:1608–1614.
38. Flamand N, Surette ME, Picard S, Bourgoin S, Borgeat P. Cyclic AMP-mediated inhibition of 5-lipoxygenase translocation and leukotriene biosynthesis in human neutrophils. *Mol Pharmacol*. 2002;62:250–256.
39. Ferreri NR, Howland WC, Stevenson DD, Spiegelberg HL. Release of leukotrienes, prostaglandins, and histamine into nasal secretions of aspirin-sensitive asthmatics during reaction to aspirin. *Am Rev Respir Dis*. 1988;137:847–854.
40. Kyrle PA, Eichler HG, Jäger U, Lechner K. Inhibition of prostacyclin and thromboxane A2 generation by low-dose aspirin at the site of plug formation in man in vivo. *Circulation*. 1987;75: 1025–1029.
41. Takami M, Tsukada W. Correlative alteration of thromboxane A2 with antigen-induced bronchoconstriction and the role of platelets as a source of TXA2 synthesis in Guinea pigs: effect of DP-1904, an inhibitor of thromboxane synthetase. *Pharmacol Res*. 1998;38:133–139.
42. Sladek K, Szczeklik A. Cysteinyl leukotrienes overproduction and mast cell activation in aspirin-provoked bronchospasm in asthma. *Eur Respir J*. 1993;6:391–399.
43. Health NIo. *Trial to Determine the Safety of Oral Ifetroban in Patients with a History of Aspirin Exacerbated Respiratory Disease*; 2015. https://clinicaltrials.gov/ct2/home.
44. Bosso JV, Schwartz LB, Stevenson DD. Tryptase and histamine release during aspirin-induced respiratory reactions. *J Allergy Clin Immunol*. 1991;88:830–837.

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45. Kay LJ, Yeo WW, Peachell PT. Prostaglandin E2 activates EP2 receptors to inhibit human lung mast cell degranulation. *Br J Pharmacol*. 2006;147:707—713.
46. Bochenek G, Kuschill-Dziurda J, Szafraniec K, Plutecka H, Szczeklik A, Nizankowska-Mogilnicka E. Certain subphenotypes of aspirin-exacerbated respiratory disease distinguished by latent class analysis. *J Allergy Clin Immunol*. 2014;133:98—103.e1—6.
47. Kupczyk M, Kurmanowska Z, Kupryś-Lipińska I, Bocheńska-Marciniak M, Kuna P. Mediators of inflammation in nasal lavage from aspirin intolerant patients after aspirin challenge. *Respir Med*. 2010;104:1404—1409.

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