Review article

Endogenous inhibitory mechanisms in asthma

Sergio E. Chiarella, MD,[a] and Peter J. Barnes, MD[b] *Rochester, Minn, and London, United Kingdom*

Endogenous inhibitory mechanisms promote resolution of inflammation, enhance tissue repair and integrity, and promote homeostasis in the lung. These mechanisms include steroid hormones, regulatory T cells, IL-10, prostaglandin E_2, prostaglandin I_2, lipoxins, resolvins, protectins, maresins, glucagon-like peptide-1 receptor, adrenomedullin, nitric oxide, and carbon monoxide. Here we review the most recent literature regarding these endogenous inhibitory mechanisms in asthma, which remain a promising target for the prevention and treatment of asthma. (J Allergy Clin Immunol Global 2023;2:100135.)

Key words: *Asthma, airway inflammation, endogenous, inhibition, inhibitory, mechanism, pathway, Treg cell, prostaglandin, lipoxin, resolving, protectin, maresin, IL-10, glucagon-like peptide-1 receptor, adrenomedullin, nitric oxide, carbon monoxide*

Abbreviations used

AHR: Airway hyperresponsiveness
AM: Adrenomedullin
CO: Carbon monoxide
EP_2: E prostanoid receptor 2
GLP-1: Glucagon-like peptide-1
GLP-1R: Glucagon-like peptide-1 receptor
11β-HSD1: 11β-Hydroxysteroid dehydrogenase type 1
HO-1: Heme oxygenase-1
ILC2: Type 2 innate lymphoid cell
LXA_4: Lipoxin A4
NO: Nitric oxide
NOS: Nitric oxide synthase
PD1: Protectin D1
PGE_2: Prostaglandin E_2
PGI_2: Prostaglandin I_2
RvD1: Resolvin D1
SNO: *S*-nitrosothiol
T2DM: Type 2 diabetes mellitus
Treg: Regulatory T

Since the publication of a review summarizing the known endogenous inhibitory mechanisms in asthma more than 20 years ago,[1] our understanding of these pathways has deepened significantly. Here we present an updated review of the endogenous inhibitory mechanisms that orchestrate the resolution of inflammation and tissue repair in asthma (Table I).[2-59] Impairment of endogenous inhibitory mechanisms may amplify the underlying inflammation in asthma, thus increasing disease severity. Understanding endogenous inhibitory mechanisms may also identify novel targets for therapy.

STEROID HORMONES

Endogenous glucocorticoids suppress inflammation in asthma through multiple molecular mechanisms, including activation of anti-inflammatory genes, repression of proinflammatory genes, and posttranscriptional modifications.[2] The diurnal patterns of endogenous glucocorticoids, such as cortisone and cortisol, are abnormal in asthmatic patients at baseline and during an exacerbation. For instance, asthmatic patients with a persistent asthma exacerbation have increased levels of serum cortisone in the afternoon compared with the levels in asthmatic patients in remission.[60] Asthmatic patients also have higher cortisol levels and cortisol-to-cortisone ratios after an inhaled allergen challenge than healthy control subjects do. In asthmatic patients, higher baseline cortisol levels were correlated with rapid recovery in FEV_1 value. Conversely, asthmatic patients with late-phase reactions had lower cortisol levels.[61] An increase in late-phase reactions was also observed after cortisol depletion in an experimental dog model of biphasic bronchoconstriction.[62] Interestingly, cortisol suppression in humans has been shown to enhance IgE-dependent inflammatory processes.[63]

Local factors in the human lung can also regulate endogenous glucocorticoid activation and inactivation.[3] For instance, 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) catalyzes the conversion of inactive cortisone to active cortisol.[64] In contrast, 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) catalyzes the inactivation of cortisol to cortisone.[4,5] Interestingly, exposure of human airway smooth muscle cells to IL-13 increased mitogen-activated protein kinase (MAPK) signaling and expression of 11β-HSD1. In turn, this led to an increase in the conversion of cortisone to cortisol and downstream glucocorticoid receptor transcriptional activity.[6] Others have demonstrated that the upregulation of epithelial 11β-HSD2 leads to impaired endogenous glucocorticoid activation, which enables the proinflammatory effects of IL-13.[7] The enzymatic regulation of the cortisone/cortisol shuttle occurs in the lung's structural cells and immune cells relevant to the pathogenesis of asthma. In murine T lymphocytes, the activation of 11β-HSD1 and the downstream increase in

From [a]the Division of Allergic Diseases, Mayo Clinic, Rochester, and [b]the National Heart and Lung Institute, Imperial College London.

Received for publication March 15, 2023; revised May 16, 2023; accepted for publication May 21, 2023.

Available online July 5, 2023.

Corresponding author: Sergio E. Chiarella, MD, Division of Allergic Diseases, Mayo Clinic, 200 First St SW, Rochester, MN 55905. E-mail: Chiarella.Sergio@mayo.edu.

The CrossMark symbol notifies online readers when updates have been made to the article such as errata or minor corrections

2772-8293

https://doi.org/10.1016/j.jacig.2023.100135

TABLE I. Endogenous inhibitory mechanisms in asthma

Endogenous inhibitory mechanism	Cellular sources	Mediator-specific effects
Steroid hormones	• Adrenal glands and gonads	• Endogenous glucocorticoids have broad anti-inflammatory effects, mainly by binding intracellular receptors and modulating gene transcription[2] • 11β-HSD1 and 11β-HSD2 regulate local levels of endogenous glucocorticoids[3-8] • Testosterone decreases the number of ILC22s and inhibits airway inflammation[9-14]
IL-10	• Treg cells, dendritic cells, macrophages, mast cells, eosinophils, neutrophils, B cells, and $ILC2_{10}$s	• Treg cells modulate the resolution of airway inflammation[15-20] • IL-10 acts on multiple cells to inhibit inflammatory pathways, including antigen presentation, eosinophil recruitment and activation, and cytokine production[21-27]
Prostaglandins	• Epithelial cells, endothelial cells, airway smooth muscle, and monocytes/macrophages	• PGE_2 acts via the EP_2 to regulates 5-lipoxygenase function and cysteinyl leukotriene production[28] • PGE_2 inhibits eosinophil migration and ILC2 activation and proliferation[28-35] • PGI_2 suppresses T_H2 cytokine expression, eosinophilia, and mucus production[36]
Lipoxins	• Epithelial cells, polymorphonuclear leukocytes, and platelets	• LXA_4 promotes the resolution of inflammation and inhibits neutrophil-endothelial cell interactions[37,38]
Resolvins	• Epithelial cells, endothelial cells, and polymorphonuclear leukocytes	• RvE1 suppresses the nuclear translocation of NF-κB and cytokine production[39] • RvE1 inhibits T_H17 cell inflammation[40] • RvD1 promotes allergen clearance[41]
Protectins	• Eosinophils	• PD1 elicits apoptotic signals in neutrophils and T cells[42] • PD1 inhibits TNF-α and IFN-γ production[42,43]
Maresins	• Macrophages, neutrophils, and platelets	• MaR1 increases Treg cells and inhibits ILC2 cytokine production[44,46] • MaR1 induces Treg formation[44]
GLP-1R	• GLP-1 is secreted by L cells in the gastrointestinal tract	• GLP-1R agonists reduce airway inflammation via a protein kinase A–dependent inactivation of NF-κB[47] • GLP-1R agonists decrease IL-33 release, numbers of ILC2s expressing IL-5 and IL-13, and expression of type 2 cytokines[48]
AM	• Epithelial cells, endothelial cells, airway smooth muscle, macrophages, and parasympathetic neural cells	• AM increases cyclic AMP in airway smooth muscle[49] and decreases AHR[50-55]
NO	• Epithelial cells, endothelial cells, macrophages, neutrophils, and mast cells	• NO functions via the stimulation of soluble guanylate cyclase to increase the production of the secondary messenger cGMP • Low levels of endogenous *S*-nitrosothiols act as a bronchodilator[56]
CO	• Epithelial cells, endothelial cells, macrophages, and fibroblasts	• HO-1–derived CO activates cGMP and promotes airway smooth muscle relaxation[57] • CO decreases the alarmin response from airway epithelial cells[58] • Administration of low-dose CO can reverse AHR[59]

cGMP, Cyclic guanosine monophosphate; *$ILC2_{10}$*, IL-10–producing ILC2; *MaR1*, maresin-1; *NF-κB*, nuclear factor-κB; *RvE1*, resolvin E1.

glucocorticoid production can modulate their differentiation, effector functions, and apoptosis.[8]

Sex steroids can also regulate airway inflammation in asthmatic patients. In humans, lower levels of testosterone are correlated with higher asthma prevalence and lower FEV_1 value.[9-11] Furthermore, the administration of nebulized dehydroepiandrosterone-3-sulfate improves disease control in patients with moderate-to-severe asthma.[12] Mechanistically, testosterone has been shown to decrease the number of lung type 2 innate lymphoid cells (ILC2s) and the expression of IL-33 and thymic stromal lymphopoietin (TSLP) in mice.[13] In addition, testosterone promotes the relaxation of airway smooth muscle via an epithelial and nitric oxide (NO)-dependent pathway.[14] Finally, progesterone can inhibit airway remodeling,

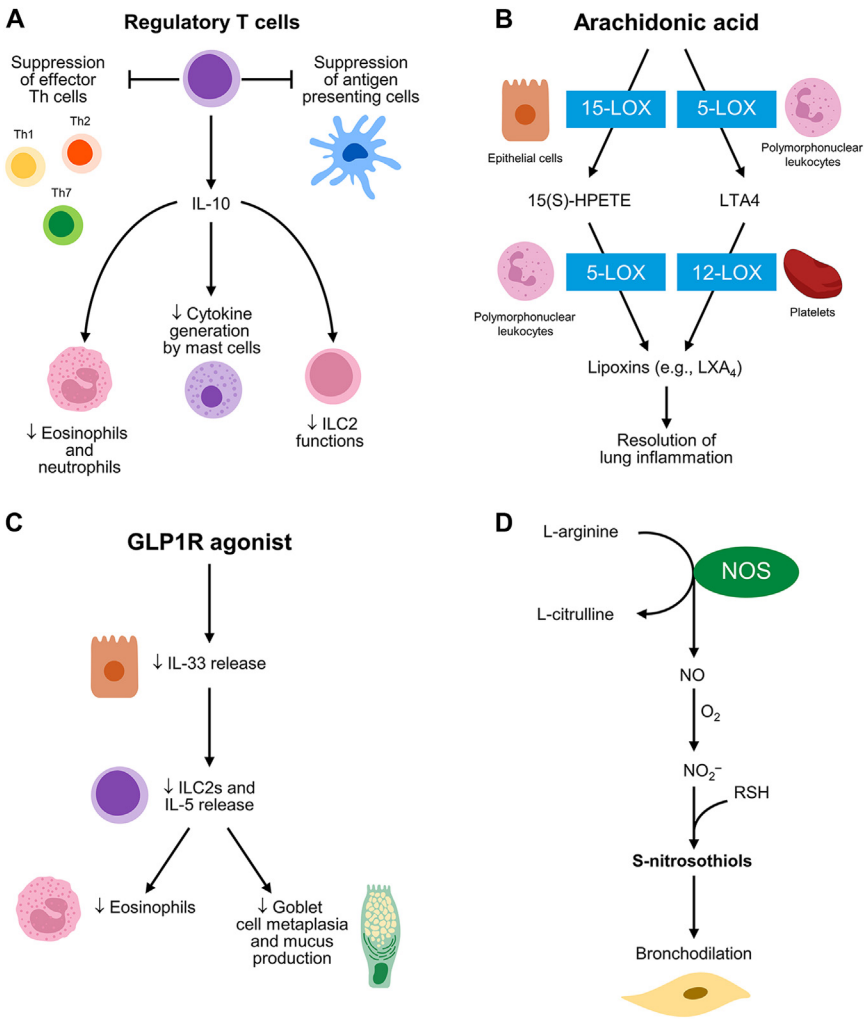

FIG 1. Endogenous inhibitory mechanisms in asthma. **A,** Treg cells promote tolerance and limit lung inflammation via the regulation of T_H cells, antigen-presenting cells, mast cells, eosinophils, and ILC2s. **B,** The biosynthesis of lipoxins from arachidonic acid by epithelial cells, polymorphonuclear leukocytes, and platelets leads to the resolution of lung inflammation. **C,** Anti-inflammatory effects of GLP1R agonism on epithelial cells, ILC2s, eosinophils, and goblet cells. **D,** Low levels of endogenous S-nitrosothiols act as a bronchodilator.

glucocorticoid resistance, and mast cell degranulation in animal studies.[65,66]

Treg CELLS AND IL-10

Regulatory T (Treg) cells are a specialized population of T cells that promote peripheral tolerance, maintain homeostasis, and limit chronic inflammation in asthma and other allergic diseases (Fig 1, *A*).[15-18] Treg cells regulate airway inflammation by releasing several cytokines, including IL-10, IL-35, TGF-β, fibrinogen-like protein 2, CD39, and CD73.[19] Treg cells can also modulate inflammation via cell contact–mediated suppression (cytotoxic T-lymphocyte antigen-4 [CTLA-4], lymphocyte activating gene-3 [LAG-3], galectin-1, and T-cell immunoglobulin and mucin domain 3 [TIM-3]).[15] Patients with moderate-to-severe asthma have a higher percentage of $CD4^+FoxP3^+$ Treg cells in their bronchoalveolar lavage fluid than do patients with mild asthma and healthy controls. Similarly, $CD4^+$ CTLA-4 and CD103 expression levels were higher in patients with moderate-to-severe asthma.[20]

IL-10, in particular, has multiple inhibitory properties that regulate the resolution of inflammation in asthmatic patients.[21] For instance, IL-10 suppresses the function of antigen-presenting cells.[22] Myelomonocytic cells exposed to IL-10 upregulate the IL-1 receptor antagonist, decreasing airway hyperreactivity and eosinophil chemotaxis.[23] IL-10 also inhibits nuclear factor-κB (NF-κB) activation in monocytes,[24] cytokine generation from bone marrow–derived mast cells,[25] pathogenic IFN-γ responses to allergens,[26] and allergen-induced neutrophil and eosinophil recruitment to the airways.[27] Although Treg cells are an important source of IL-10, other cells, including dendritic cells, macrophages, mast cells, eosinophils, neutrophils, and B cells, can also produce this inhibitory cytokine.[67] Interestingly, IL-10–producing ILC2s ($ILC2_{10}$s) have recently been identified.[68] In mice, $ILC2_{10}$s suppress proinflammatory ILC2 effector functions and regulate allergic lung inflammation.[69]

Bronchoalveolar lavage fluid from asthmatic patients has lower levels of IL-10 than in bronchoalveolar lavage fluid from nonasthmatic controls[70]; similarly, PBMCs of asthmatic patients produce less IL-10 at baseline and when simulated.[71] In addition, alveolar macrophages from asthmatic patients release a lower amount of IL-10 at baseline and after IL-1β stimulation than do those from nonasthmatic patients.[72] Glucocorticoid-induced IL-10 release from $CD4^+$ T lymphocytes is also defective in asthmatic patients.[73] Finally, specific IL-10 polymorphisms are associated with an increased asthma prevalence in adults.[74] Furthermore, compared with controls. patients with severe asthma are less likely to have the putative high–IL-10–producing haplotype and more likely to have the putative low–IL-10–producing haplotype.[75]

Multiple studies have proved the importance of Treg cells in regulating immune tolerance in the lung. For instance, the expansion of Treg cells via a TNF receptor superfamily member 25 (TNFR25)-specific mAb led to the suppression of allergic lung inflammation in mice, including inhibition of T_H2 cytokine production.[76] Treg cells are also important in regulating the priming responses to allergens, as demonstrated by an article showing that depletion of Treg cells during the sensitization phase led to augmented allergic airway inflammation in mice.[77] Interestingly, depletion of Treg cells during the elicitation phase did not have a similar effect.[78] These results contrast with those of other murine studies showing that the adoptive transfer of Treg cells during an allergen challenge attenuates airway inflammation.[79]

PROSTAGLANDINS AND LIPOXINS

Certain prostaglandins and lipoxins can also promote the resolution of allergic lung inflammation (Fig 1, *B*). Prostaglandin E_2 (PGE_2) is a naturally occurring prostaglandin that acts via the E prostanoid receptor 2 (EP_2) to inhibit 5-lipoxygenase function and cysteinyl leukotriene (CysLT) production.[28] In a murine model of allergic asthma, the PGE_2-EP_2 axis, specifically in T cells, inhibited allergic airway inflammation. EP_2 knockout mice had worse airway inflammation than wild-type controls did. Furthermore, administering a PGE_2 analog protected wild-type mice against airway inflammation but not EP_2 knockout mice.[29] Specifically, PGE_2 protects against allergic lung inflammation by regulating macrophage polarization,[30] inhibiting eosinophil migration and activation,[31,32] and limiting ILC2 proliferation and activation.[33,34] Moreover, human PMNs exposed to PGE_2 switched eicosanoid biosynthesis from leukotriene E_4 (LTE_4) to lipoxin A4 (LXA_4), which was associated with resolution of inflammation.[35] In addition, LXA_4 inhibits PMN-endothelial cell interactions.[37] Finally, in a rat model of allergic asthma using *Angiostrongylus costaricensis*, cyclooxygenase-2–derived PGE_2 and LXA_4 promoted the resolution of allergic edema.[38]

Sputum PGE_2 level is higher in asthmatic patients than in healthy controls. A decreased PGE_2-to– cysteinyl leukotriene ratio may promote airway remodeling and worse lung function in humans.[80] Level of LXA_4 in exhaled breath condensate was elevated in all severities of asthma, but the LXA_4/LTB_4 ratio in exhaled breath concentrate was lower in patients with severe asthma than in patients with moderate asthma.[81] Notably, there have been several clinical trials aimed at administering arachidonic acid–derived inhibitory mediators for the treatment of asthma,[82] including PGE_2,[83-86] and LXA_4.[87,88] For instance, LXA_4 inhalation in asthmatic patients decreased LTC_4-induced bronchoconstriction.[87] Novel synthetic compounds to regulate these pathways, such as the selective formyl peptide receptor type 2 (FPR2)/LXA_4 receptor agonist ACT-389949,[89] are also under development.

Prostaglandin I_2 (PGI_2), also known as prostacyclin, is another prostaglandin that promotes the resolution of inflammation. PGI_2 suppresses T_H2 cytokine expression, eosinophilia, and mucus production in an ovalbumin murine model of asthma. Also in mice, cicaprost (a PGI_2 analog) inhibits IL-33–driven T_H2 cytokines by $CD4^+$ T cells in a PGI_2 receptor–specific manner.[36]

RESOLVINS, PROTECTINS, AND MARESINS

Docosahexaenoic acid–derived lipid mediators, such as resolvins, protectins, and maresins, also promote tissue homeostasis and the resolution of lung inflammation. For instance, in a murine model of asthma, resolvin E1 (RvE1) inhibits the production of IL-6 and IL-23, both of which are integral components of T_H17 cell inflammation and the response to allergens.[40] Resolvin D1 (RvD1) promotes the resolution of lung eosinophilia in a murine model of airway inflammation. Furthermore, aspirin-triggered RvD1 (AT-RvD1) enhances murine macrophage phagocytosis and allergen clearance.[41] Protectin D1 (PD1) is generated by T_H2 cell–skewed PBMCs via a 15-lipoxygenase-1–dependent pathway and elicits apoptotic signals in human neutrophils and T cells.[42] Finally, maresin-1 promotes the resolution of inflammation by increasing Treg cells, resulting in the downstream inhibition of ILC2 activation and cytokine production.[44] In addition, maresin-1 suppresses proinflammatory signals from human bronchial epithelial cells, enhances tissue regeneration, and favors a return to homeostasis.[45,46]

GLUCAGON-LIKE PEPTIDE-1 RECEPTOR

Glucagon-like peptide-1 (GLP-1) is an incretin hormone secreted by L cells in the gastrointestinal tract. GLP-1 receptor (GLP-1R) agonists potentiate glucose-dependent insulin secretion and were initially developed for managing type 2 diabetes mellitus (T2DM). More recently, GLP-1R agonism has been recognized as a novel endogenous inhibitory pathway in asthma (Fig 1, *C*). Zhu et al[47] initially demonstrated that treatment with a GLP-1R agonist led to a significant reduction in airway inflammation and mucus secretion in a murine model of asthma. Furthermore, Zhu et al[47] showed that these effects were mediated by the protein kinase A–dependent inactivation of nuclear factor-κB. Similar findings were observed in obese mice, with decreased airway eosinophilic inflammation and airway hyperresponsiveness (AHR) in the group treated with GLP-1R agonist. Hur et al show that these findings were mediated by IL-1β and the NLRP3 inflammasome.[90] Notably, in an *Alternaria* extract model of allergic inflammation, GLP-1R agonist treatment led to reductions in IL-33 release, the numbers of ILC2s expressing IL-5 and IL-13, expression of type 2 cytokines and chemokines, airway eosinophilia, mucus secretion, and AHR.[48]

Others have shown that GLP-1Rs are expressed in human eosinophils and neutrophils and that GLP-1R agonist treatment decreases LPS-induced eosinophil activation.[91] Furthermore, the GLP-1R agonist exendin-4 reduced human bronchial hyperreactivity in an epithelium-independent and cyclic AMP–dependent protein kinase A pathway.[92] In a more recent publication involving patients with asthma and T2DM, Foer et al found that the asthma exacerbation rate and asthma symptoms were lower

in those initiating GLP-1 therapy than in those using other medications to manage T2DM, such as insulin or sulfonylureas.[93] The effects of GLP-1 therapy were independent of the improvement in glycemic control and weight loss. Others have also shown the beneficial effects of GLP-1 therapy on the lung function of asthmatic patients with T2DM.[94] These promising studies highlight the use of GLP-1R agonists as a novel treatment strategy for asthmatic patients with metabolic dysfunction.

AM

Adrenomedullin (AM) is a 33–amino acid vasodilator peptide with multiple biologic effects on health and disease. AM is expressed in several cell populations of the human lung, including epithelial, smooth muscle, endothelial, alveolar macrophage, and parasympathetic neural cells.[50,51] Hagner et al showed that chronic allergic inflammation reduced AM in airway epithelial and endothelial cells in 2 distinct murine models of asthma.[52] Interestingly, the administration of AM resulted in a decrease in ovalbumin-induced AHR. An AM receptor antagonist reversed these effects of AM. In addition, Hagner et al demonstrated that AM increased wound repair in human and mouse *ex vivo* studies.[52] Others have shown that the genetic loss of AM led to an increase in airway smooth muscle hyperplasia and AHR in a murine model of asthma. In this model, AM-deficient mice did not have changes in level of immunoglobulin, level of type 2 cytokines, eosinophilia, or airway secretion.[53] In guinea pigs, AM has been shown to induce a dose-dependent inhibition of acetylcholine- and histamine-induced bronchoconstriction.[54] Moreover, AM can also inhibit the secretion of the cytokine-induced neutrophil chemoattractant from LPS-stimulated rat alveolar macrophages.[55] Interestingly, plasma AM levels increase as asthma severity progresses and are negatively correlated with FEV_1 value in asthmatic patients.[95]

NO

Endogenous NO is a principal regulator of airway function in humans.[96] NO is generated during the conversion of L-arginine to L-citrulline by NO synthase (NOS). High levels of NO lead to the detrimental oxidation and nitration of proteins, with downstream effects on airway inflammation. In contrast, low levels of endogenous *S*-nitrosothiols (SNOs) are beneficial and act as a bronchodilator (Fig 1, *D*).[56] In this regard, a study showed that wild-type mice with AHR have low levels of lung SNOs and increased levels of GSNO reductase (GSNOR). Interestingly, GSNOR knockout mice have higher lung SNOs and are protected against AHR.[97] NO can also have a protective role in the upper airways.[98] Physiologic levels of endogenous NO have also been shown to suppress plasma leakage in rats, whereas NO production associated with inducible NOS increases plasma leakage.[99] Evidence of the bronchoprotective effects of NO arise from a study of the effects of NG-nitro-L-arginine methyl ester (L-NAME), a nonselective NOS inhibitor; in which the administration of nebulized L-NAME to subjects increased AHR.[100] In contrast, another human study found that inhibiting endogenous NO does not affect the allergen-induced early and late asthmatic responses.[101]

CO

The primary source of endogenous carbon monoxide (CO) is the catabolism of hemoglobin by heme oxygenase-1 (HO-1).[102] The HO-1–CO axis has been recognized as having protective roles.[103] The HO-1 products CO and bilirubin decrease the NOD-like receptor protein 3 (NLRP3)-retinoid X receptor (RXR) axis in human airway epithelial cells. In addition, HO-1 decreases the production of IL-25, IL-33, and TSLP, which are key alarmins in asthma, both in human airway epithelial cells and mice.[58] The HO pathway has also been shown to have protective effects by inhibiting airway inflammation, oxidate stress, and AHR in a guinea pig model of asthma.[104] Similarly, low-dose CO can reverse AHR in a murine model of asthma, irrespective of the presence of airway inflammation.[59] HO-1–derived CO can also relax airway smooth muscle by activating guanylyl cyclase and generating cyclic guanosine monophosphate.[57] Notably, asthmatic patients have higher levels of exhaled CO and HO-1.[105]

In conclusion, in the past 2 decades, we have seen a notable advance in our understanding of the endogenous inhibitory pathways in asthma. Novel mechanisms are being explored, such as the transmembrane protein 178, which negatively regulates calcium responses and inflammatory signals in airway epithelial cells.[106] Nevertheless, there are still significant gaps in our knowledge and ability to leverage these pathways for the treatment of asthma and restoration of lung homeostasis. Therefore, further research in this critical aspect of asthma pathogenesis is warranted. These future studies should also explore the interactions and synergy between the various endogenous inhibitory mechanisms.

DISCLOSURE STATEMENT

Supported by the National Institute of Allergy and Infectious Diseases, National Institutes of Health (grant K08AI141765) and the 2022 American Academy of Audiology, Asthma & Immunology Foundation and Donald Y.M. Young, MD, FAAAI, Faculty Development Award (to S.E.C.).

Disclosure of potential conflict of interest: The authors declare that they have no relevant conflicts of interest.

REFERENCES

1. Barnes PJ. Endogenous inhibitory mechanisms in asthma. Am J Respir Crit Care Med 2000;161:S176-81.
2. Barnes PJ. Glucocorticosteroids: current and future directions. Br J Pharmacol 2011;163:29-43.
3. Schleimer RP. Potential regulation of inflammation in the lung by local metabolism of hydrocortisone. Am J Respir Cell Mol Biol 1991;4:166-73.
4. Blum A, Maser E. Enzymology and molecular biology of glucocorticoid metabolism in humans. Prog Nucleic Acid Res Mol Biol 2003;75:173-216.
5. Tomlinson JW, Walker EA, Bujalska IJ, Draper N, Lavery GG, Cooper MS, et al. 11beta-hydroxysteroid dehydrogenase type 1: a tissue-specific regulator of glucocorticoid response. Endocr Rev 2004;25:831-66.
6. Hu A, Fatma S, Cao J, Grunstein JS, Nino G, Grumbach Y, et al. Th2 cytokine-induced upregulation of 11beta-hydroxysteroid dehydrogenase-1 facilitates glucocorticoid suppression of proasthmatic airway smooth muscle function. Am J Physiol Lung Cell Mol Physiol 2009;296:L790-803.
7. Josephson MB, Jiao J, Xu S, Hu A, Paranjape C, Grunstein JS, et al. IL-13-induced changes in endogenous glucocorticoid metabolism in the lung regulate the proasthmatic response. Am J Physiol Lung Cell Mol Physiol 2012;303:L382-90.
8. Zhang TY, Ding X, Daynes RA. The expression of 11 beta-hydroxysteroid dehydrogenase type I by lymphocytes provides a novel means for intracrine regulation of glucocorticoid activities. J Immunol 2005;174:879-89.
9. Bulkhi AA, Shepard KV 2nd, Casale TB, Cardet JC. Elevated testosterone is associated with decreased likelihood of current asthma regardless of sex. J Allergy Clin Immunol Pract 2020;8:3029-35.e4.
10. Mohan SS, Knuiman MW, Divitini ML, James AL, Musk AW, Handelsman DJ, et al. Higher serum testosterone and dihydrotestosterone, but not oestradiol, are

independently associated with favourable indices of lung function in community-dwelling men. Clin Endocrinol (Oxf) 2015;83:268-76.
11. Svartberg J, Schirmer H, Medbo A, Melbye H, Aasebo U. Reduced pulmonary function is associated with lower levels of endogenous total and free testosterone. The Tromso study. Eur J Epidemiol 2007;22:107-12.
12. Wenzel SE, Robinson CB, Leonard JM, Panettieri RA Jr. Nebulized dehydroepiandrosterone-3-sulfate improves asthma control in the moderate-to-severe asthma results of a 6-week, randomized, double-blind, placebo-controlled study. Allergy Asthma Proc 2010;31:461-71.
13. Cephus JY, Stier MT, Fuseini H, Yung JA, Toki S, Bloodworth MH, et al. Testosterone attenuates group 2 innate lymphoid cell-mediated airway inflammation. Cell Rep 2017;21:2487-99.
14. Espinoza J, Montano LM, Perusquia M. Nongenomic bronchodilating action elicited by dehydroepiandrosterone (DHEA) in a guinea pig asthma model. J Steroid Biochem Mol Biol 2013;138:174-82.
15. Khan MA. Regulatory T cells mediated immunomodulation during asthma: a therapeutic standpoint. J Transl Med 2020;18:456.
16. Palomares O, Yaman G, Azkur AK, Akkoc T, Akdis M, Akdis CA. Role of Treg in immune regulation of allergic diseases. Eur J Immunol 2010;40:1232-40.
17. Pellerin L, Jenks JA, Begin P, Bacchetta R, Nadeau KC. Regulatory T cells and their roles in immune dysregulation and allergy. Immunol Res 2014;58:358-68.
18. Zhang H, Kong H, Zeng X, Guo L, Sun X, He S. Subsets of regulatory T cells and their roles in allergy. J Transl Med 2014;12:125.
19. Thorburn AN, Hansbro PM. Harnessing regulatory T cells to suppress asthma: from potential to therapy. Am J Respir Cell Mol Biol 2010;43:511-9.
20. Smyth LJ, Eustace A, Kolsum U, Blaikely J, Singh D. Increased airway T regulatory cells in asthmatic subjects. Chest 2010;138:905-12.
21. Ogawa Y, Duru EA, Ameredes BT. Role of IL-10 in the resolution of airway inflammation. Curr Mol Med 2008;8:437-45.
22. Fiorentino DF, Zlotnik A, Mosmann TR, Howard M, O'Garra A. IL-10 inhibits cytokine production by activated macrophages. J Immunol 1991;147:3815-22.
23. Kline JN, Fisher PA, Monick MM, Hunninghake GW. Regulation of interleukin-1 receptor antagonist by Th1 and Th2 cytokines. Am J Physiol 1995;269:L92-8.
24. Wang P, Wu P, Siegel MI, Egan RW, Billah MM. Interleukin (IL)-10 inhibits nuclear factor kappa B (NF kappa B) activation in human monocytes. IL-10 and IL-4 suppress cytokine synthesis by different mechanisms. J Biol Chem 1995;270:9558-63.
25. Arock M, Zuany-Amorim C, Singer M, Benhamou M, Pretolani M. Interleukin-10 inhibits cytokine generation from mast cells. Eur J Immunol 1996;26:166-70.
26. Branchett WJ, Stolting H, Oliver RA, Walker SA, Puttur F, Gregory LG, et al. A T cell-myeloid IL-10 axis regulates pathogenic IFN-gamma-dependent immunity in a mouse model of type 2-low asthma. J Allergy Clin Immunol 2020;145:666-78.e9.
27. Zuany-Amorim C, Haile S, Leduc D, Dumarey C, Huerre M, Vargaftig BB, et al. Interleukin-10 inhibits antigen-induced cellular recruitment into the airways of sensitized mice. J Clin Invest 1995;95:2644-51.
28. Rusznak M, Peebles RS Jr. Prostaglandin E2 in NSAID-exacerbated respiratory disease: protection against cysteinyl leukotrienes and group 2 innate lymphoid cells. Curr Opin Allergy Clin Immunol 2019;19:38-45.
29. Zaslona Z, Okunishi K, Bourdonnay E, Domingo-Gonzalez R, Moore BB, Lukacs NW, et al. Prostaglandin E(2) suppresses allergic sensitization and lung inflammation by targeting the E prostanoid 2 receptor on T cells. J Allergy Clin Immunol 2014;133:379-87.
30. Draijer C, Boorsma CE, Reker-Smit C, Post E, Poelstra K, Melgert BN. PGE2-treated macrophages inhibit development of allergic lung inflammation in mice. J Leukoc Biol 2016;100:95-102.
31. Konya V, Philipose S, Balint Z, Olschewski A, Marsche G, Sturm EM, et al. Interaction of eosinophils with endothelial cells is modulated by prostaglandin EP4 receptors. Eur J Immunol 2011;41:2379-89.
32. Sturm EM, Schratl P, Schuligoi R, Konya V, Sturm GJ, Lippe IT, et al. Prostaglandin E2 inhibits eosinophil trafficking through E-prostanoid 2 receptors. J Immunol 2008;181:7273-83.
33. Maric J, Ravindran A, Mazzurana L, Bjorklund AK, Van Acker A, Rao A, et al. Prostaglandin E2 suppresses human group 2 innate lymphoid cell function. J Allergy Clin Immunol 2018;141:1761-73.e6.
34. Zhou Y, Wang W, Zhao C, Wang Y, Wu H, Sun X, et al. Prostaglandin E2 inhibits group 2 innate lymphoid cell activation and allergic airway inflammation through E-prostanoid 4-cyclic adenosine monophosphate signaling. Front Immunol 2018;9:501.
35. Levy BD, Clish CB, Schmidt B, Gronert K, Serhan CN. Lipid mediator class switching during acute inflammation: signals in resolution. Nat Immunol 2001;2:612-9.
36. Zhou W, Zhang J, Toki S, Goleniewska K, Johnson MO, Bloodworth MH, et al. The PGI2 analog cicaprost inhibits IL-33-induced Th2 responses, IL-2 production, and CD25 expression in mouse CD4(+) T Cells. J Immunol 2018;201:1936-45.
37. Papayianni A, Serhan CN, Brady HR. Lipoxin A4 and B4 inhibit leukotriene-stimulated interactions of human neutrophils and endothelial cells. J Immunol 1996;156:2264-72.
38. Bandeira-Melo C, Serra MF, Diaz BL, Cordeiro RS, Silva PM, Lenzi HL, et al. Cyclooxygenase-2-derived prostaglandin E2 and lipoxin A4 accelerate resolution of allergic edema in Angiostrongylus costaricensis-infected rats: relationship with concurrent eosinophilia. J Immunol 2000;164:1029-36.
39. Flesher RP, Herbert C, Kumar RK. Resolvin E1 promotes resolution of inflammation in a mouse model of an acute exacerbation of allergic asthma. Clin Sci (Lond) 2014;126:805-14.
40. Haworth O, Cernadas M, Yang R, Serhan CN, Levy BD. Resolvin E1 regulates interleukin 23, interferon-gamma and lipoxin A4 to promote the resolution of allergic airway inflammation. Nat Immunol 2008;9:873-9.
41. Rogerio AP, Haworth O, Croze R, Oh SF, Uddin M, Carlo T, et al. Resolvin D1 and aspirin-triggered resolvin D1 promote resolution of allergic airways responses. J Immunol 2012;189:1983-91.
42. Ariel A, Li PL, Wang W, Tang WX, Fredman G, Hong S, et al. The docosatriene protectin D1 is produced by TH2 skewing and promotes human T cell apoptosis via lipid raft clustering. J Biol Chem 2005;280:43079-86.
43. Ariel A, Fredman G, Sun YP, Kantarci A, Van Dyke TE, Luster AD, et al. Apoptotic neutrophils and T cells sequester chemokines during immune response resolution through modulation of CCR5 expression. Nat Immunol 2006;7:1209-16.
44. Krishnamoorthy N, Burkett PR, Dalli J, Abdulnour RE, Colas R, Ramon S, et al. Cutting edge: maresin-1 engages regulatory T cells to limit type 2 innate lymphoid cell activation and promote resolution of lung inflammation. J Immunol 2015;194:863-7.
45. Nordgren TM, Heires AJ, Wyatt TA, Poole JA, LeVan TD, Cerutis DR, et al. Maresin-1 reduces the pro-inflammatory response of bronchial epithelial cells to organic dust. Respir Res 2013;14:51.
46. Serhan CN, Dalli J, Karamnov S, Choi A, Park CK, Xu ZZ, et al. Macrophage proresolving mediator maresin 1 stimulates tissue regeneration and controls pain. FASEB J 2012;26:1755-65.
47. Zhu T, Wu XL, Zhang W, Xiao M. Glucagon Like Peptide-1 (GLP-1) Modulates OVA-induced airway inflammation and mucus secretion involving a protein kinase A (PKA)-dependent nuclear factor-kappaB (NF-kappaB) signaling pathway in mice. Int J Mol Sci 2015;16:20195-211.
48. Toki S, Goleniewska K, Reiss S, Zhang J, Bloodworth MH, Stier MT, et al. Glucagon-like peptide 1 signaling inhibits allergen-induced lung IL-33 release and reduces group 2 innate lymphoid cell cytokine production in vivo. J Allergy Clin Immunol 2018;142:1515-28.e8.
49. Mandal J, Roth M, Papakonstantinou E, Fang L, Savic S, Tamm M, et al. Adrenomedullin mediates pro-angiogenic and pro-inflammatory cytokines in asthma and COPD. Pulm Pharmacol Ther 2019;56:8-14.
50. Martinez A, Miller MJ, Unsworth EJ, Siegfried JM, Cuttitta F. Expression of adrenomedullin in normal human lung and in pulmonary tumors. Endocrinology 1995;136:4099-105.
51. Kubo A, Minamino N, Isumi Y, Katafuchi T, Kangawa K, Dohi K, et al. Production of adrenomedullin in macrophage cell line and peritoneal macrophage. J Biol Chem 1998;273:16730-8.
52. Hagner S, Welz H, Kicic A, Alrifai M, Marsh LM, Sutanto EN, et al. Suppression of adrenomedullin contributes to vascular leakage and altered epithelial repair during asthma. Allergy 2012;67:998-1006.
53. Yamamoto H, Nagase T, Shindo T, Teramoto S, Aoki-Nagase T, Yamaguchi Y, et al. Adrenomedullin insufficiency increases allergen-induced airway hyperresponsiveness in mice. J Appl Physiol (1985) 2007;102:2361-8.
54. Kanazawa H, Kurihara N, Hirata K, Kudoh S, Kawaguchi T, Takeda T. Adrenomedullin, a newly discovered hypotensive peptide, is a potent bronchodilator. Biochem Biophys Res Commun 1994;205:251-4.
55. Kamoi H, Kanazawa H, Hirata K, Kurihara N, Yano Y, Otani S. Adrenomedullin inhibits the secretion of cytokine-induced neutrophil chemoattractant, a member of the interleukin-8 family, from rat alveolar macrophages. Biochem Biophys Res Commun 1995;211:1031-5.
56. Ghosh S, Erzurum SC. Nitric oxide metabolism in asthma pathophysiology. Biochim Biophys Acta 2011;1810:1008-16.
57. Kinhult J, Uddman R, Cardell LO. The induction of carbon monoxide-mediated airway relaxation by PACAP 38 in isolated guinea pig airways. Lung 2001;179:1-8.
58. Lv J, Su W, Yu Q, Zhang M, Di C, Lin X, et al. Heme oxygenase-1 protects airway epithelium against apoptosis by targeting the proinflammatory NLRP3-RXR axis in asthma. J Biol Chem 2018;293:18454-65.
59. Ameredes BT, Otterbein LE, Kohut LK, Gligonic AL, Calhoun WJ, Choi AM. Low-dose carbon monoxide reduces airway hyperresponsiveness in mice. Am J Physiol Lung Cell Mol Physiol 2003;285:L1270-6.

60. Fujitaka M, Nomura S, Sakura N, Ueda K, Matuura R, Yumiba C. Morning and afternoon serum levels of cortisone and cortisol in asthmatic patients. Clin Chim Acta 2000;299:101-8.
61. Peebles RS Jr, Togias A, Bickel CA, Diemer FB, Hubbard WC, Schleimer RP. Endogenous glucocorticoids and antigen-induced acute and late phase pulmonary responses. Clin Exp Allergy 2000;30:1257-65.
62. Sasaki H, Yanai M, Shimura S, Okayama H, Aikawa T, Sasaki T, et al. Late asthmatic response to Ascaris antigen challenge in dogs treated with metyrapone. Am Rev Respir Dis 1987;136:1459-65.
63. Herrscher RF, Kasper C, Sullivan TJ. Endogenous cortisol regulates immunoglobulin E-dependent late phase reactions. J Clin Invest 1992;90:596-603.
64. Morgan SA, McCabe EL, Gathercole LL, Hassan-Smith ZK, Larner DP, Bujalska IJ, et al. 11beta-HSD1 is the major regulator of the tissue-specific effects of circulating glucocorticoid excess. Proc Natl Acad Sci U S A 2014;111:E2482-91.
65. Vasiadi M, Kempuraj D, Boucher W, Kalogeromitros D, Theoharides TC. Progesterone inhibits mast cell secretion. Int J Immunopathol Pharmacol 2006;19:787-94.
66. Zhang X, Bao W, Fei X, Zhang Y, Zhang G, Zhou X, et al. Progesterone attenuates airway remodeling and glucocorticoid resistance in a murine model of exposing to ozone. Mol Immunol 2018;96:69-77.
67. Rutz S, Ouyang W. Regulation of interleukin-10 expression. Adv Exp Med Biol 2016;941:89-116.
68. Sun H, Wu Y, Zhang Y, Ni B. IL-10-Producing ILCs: Molecular mechanisms and disease relevance. Front Immunol 2021;12:650200.
69. Howard E, Lewis G, Galle-Treger L, Hurrell BP, Helou DG, Shafiei-Jahani P, et al. IL-10 production by ILC2s requires Blimp-1 and cMaf, modulates cellular metabolism, and ameliorates airway hyperreactivity. J Allergy Clin Immunol 2021;147:1281-95.e5.
70. Gupta A, Dimeloe S, Richards DF, Chambers ES, Black C, Urry Z, et al. Defective IL-10 expression and in vitro steroid-induced IL-17A in paediatric severe therapy-resistant asthma. Thorax 2014;69:508-15.
71. Borish L, Aarons A, Rumbyrt J, Cvietusa P, Negri J, Wenzel S. Interleukin-10 regulation in normal subjects and patients with asthma. J Allergy Clin Immunol 1996;97:1288-96.
72. John M, Lim S, Seybold J, Jose P, Robichaud A, O'Connor B, et al. Inhaled corticosteroids increase interleukin-10 but reduce macrophage inflammatory protein-1alpha, granulocyte-macrophage colony-stimulating factor, and interferon-gamma release from alveolar macrophages in asthma. Am J Respir Crit Care Med 1998;157:256-62.
73. Hawrylowicz C, Richards D, Loke TK, Corrigan C, Lee T. A defect in corticosteroid-induced IL-10 production in T lymphocytes from corticosteroid-resistant asthmatic patients. J Allergy Clin Immunol 2002;109:369-70.
74. Hyun MH, Lee CH, Kang MH, Park BK, Lee YH. Interleukin-10 promoter gene polymorphisms and susceptibility to asthma: a meta-analysis. PLoS One 2013;8:e53758.
75. Lim S, Crawley E, Woo P, Barnes PJ. Haplotype associated with low interleukin-10 production in patients with severe asthma. Lancet 1998;352:113.
76. Schreiber TH, Wolf D, Tsai MS, Chirinos J, Deyev VV, Gonzalez L, et al. Therapeutic Treg expansion in mice by TNFRSF25 prevents allergic lung inflammation. J Clin Invest 2010;120:3629-40.
77. Baru AM, Hartl A, Lahl K, Krishnaswamy JK, Fehrenbach H, Yildirim AO, et al. Selective depletion of Foxp3+ Treg during sensitization phase aggravates experimental allergic airway inflammation. Eur J Immunol 2010;40:2259-66.
78. Baru AM, Ganesh V, Krishnaswamy JK, Hesse C, Untucht C, Glage S, et al. Absence of Foxp3+ regulatory T cells during allergen provocation does not exacerbate murine allergic airway inflammation. PLoS One 2012;7:e47102.
79. Xu W, Lan Q, Chen M, Chen H, Zhu N, Zhou X, et al. Adoptive transfer of induced-Treg cells effectively attenuates murine airway allergic inflammation. PLoS One 2012;7:e40314.
80. Aggarwal S, Moodley YP, Thompson PJ, Misso NL. Prostaglandin E2 and cysteinyl leukotriene concentrations in sputum: association with asthma severity and eosinophilic inflammation. Clin Exp Allergy 2010;40:85-93.
81. Kazani S, Planaguma A, Ono E, Bonini M, Zahid M, Marigowda G, et al. Exhaled breath condensate eicosanoid levels associate with asthma and its severity. J Allergy Clin Immunol 2013;132:547-53.
82. Insuela DBR, Ferrero MR, Coutinho DS, Martins MA, Carvalho VF. Could arachidonic acid-derived pro-resolving mediators be a new therapeutic strategy for asthma therapy? Front Immunol 2020;11:580598.
83. Kawakami Y, Uchiyama K, Irie T, Murao M. Evaluation of aerosols of prostaglandins E1 and E2 as bronchodilators. Eur J Clin Pharmacol 1973;6:127-32.
84. Melillo E, Woolley KL, Manning PJ, Watson RM, O'Byrne PM. Effect of inhaled PGE2 on exercise-induced bronchoconstriction in asthmatic subjects. Am J Respir Crit Care Med 1994;149:1138-41.
85. Pavord ID, Tattersfield AE. Bronchoprotective role for endogenous prostaglandin E2. Lancet 1995;345:436-8.
86. Pavord ID, Wong CS, Williams J, Tattersfield AE. Effect of inhaled prostaglandin E2 on allergen-induced asthma. Am Rev Respir Dis 1993;148:87-90.
87. Christie PE, Spur BW, Lee TH. The effects of lipoxin A4 on airway responses in asthmatic subjects. Am Rev Respir Dis 1992;145:1281-4.
88. Kong X, Wu SH, Zhang L, Chen XQ. Pilot application of lipoxin A4 analog and lipoxin A4 receptor agonist in asthmatic children with acute episodes. Exp Ther Med 2017;14:2284-90.
89. Stalder AK, Lott D, Strasser DS, Cruz HG, Krause A, Groenen PM, et al. Biomarker-guided clinical development of the first-in-class anti-inflammatory FPR2/ALX agonist ACT-389949. Br J Clin Pharmacol 2017;83:476-86.
90. Hur J, Kang JY, Kim YK, Lee SY, Lee HY. Glucagon-like peptide 1 receptor (GLP-1R) agonist relieved asthmatic airway inflammation via suppression of NLRP3 inflammasome activation in obese asthma mice model. Pulm Pharmacol Ther 2021;67:102003.
91. Mitchell PD, Salter BM, Oliveria JP, El-Gammal A, Tworek D, Smith SG, et al. Glucagon-like peptide-1 receptor expression on human eosinophils and its regulation of eosinophil activation. Clin Exp Allergy 2017;47:331-8.
92. Rogliani P, Calzetta L, Capuani B, Facciolo F, Cazzola M, Lauro D, et al. Glucagon-like peptide 1 receptor: a novel pharmacological target for treating human bronchial hyperresponsiveness. Am J Respir Cell Mol Biol 2016;55:804-14.
93. Foer D, Beeler PE, Cui J, Karlson EW, Bates DW, Cahill KN. Asthma exacerbations in patients with type 2 diabetes and asthma on glucagon-like peptide-1 receptor agonists. Am J Respir Crit Care Med 2021;203:831-40.
94. Rogliani P, Matera MG, Calzetta L, Hanania NA, Page C, Rossi I, et al. Long-term observational study on the impact of GLP-1R agonists on lung function in diabetic patients. Respir Med 2019;154:86-92.
95. Ceyhan BB, Karakurt S, Hekim N. Plasma adrenomedullin levels in asthmatic patients. J Asthma 2001;38:221-7.
96. Barnes PJ. NO or no NO in asthma? Thorax 1996;51:218-20.
97. Que LG, Liu L, Yan Y, Whitehead GS, Gavett SH, Schwartz DA, et al. Protection from experimental asthma by an endogenous bronchodilator. Science 2005;308:1618-21.
98. Maniscalco M, Sofia M, Pelaia G. Nitric oxide in upper airways inflammatory diseases. Inflamm Res 2007;56:58-69.
99. Bernareggi M, Mitchell JA, Barnes PJ, Belvisi MG. Dual action of nitric oxide on airway plasma leakage. Am J Respir Crit Care Med 1997;155:869-74.
100. Taylor DA, McGrath JL, Orr LM, Barnes PJ, O'Connor BJ. Effect of endogenous nitric oxide inhibition on airway responsiveness to histamine and adenosine-5′-monophosphate in asthma. Thorax 1998;53:483-9.
101. Taylor DA, McGrath JL, O'Connor BJ, Barnes PJ. Allergen-induced early and late asthmatic responses are not affected by inhibition of endogenous nitric oxide. Am J Respir Crit Care Med 1998;158:99-106.
102. Kharitonov SA, Barnes PJ. Exhaled markers of pulmonary disease. Am J Respir Crit Care Med 2001;163:1693-722.
103. Carter EP, Garat C, Imamura M. Continual emerging roles of HO-1: protection against airway inflammation. Am J Physiol Lung Cell Mol Physiol 2004;287:L24-5.
104. Almolki A, Taille C, Martin GF, Jose PJ, Zedda C, Conti M, et al. Heme oxygenase attenuates allergen-induced airway inflammation and hyperreactivity in guinea pigs. Am J Physiol Lung Cell Mol Physiol 2004;287:L26-34.
105. Horvath I, Donnelly LE, Kiss A, Paredi P, Kharitonov SA, Barnes PJ. Raised levels of exhaled carbon monoxide are associated with an increased expression of heme oxygenase-1 in airway macrophages in asthma: a new marker of oxidative stress. Thorax 1998;53:668-72.
106. Patel NB, Ostilla LA, Cuervo-Pardo L, Berdnikovs S, Chiarella SE. Gene expression of TMEM178, which encodes a negative regulator of NFATc1, decreases with the progression of asthma severity. Clin Transl Allergy 2019;9:38.