Could Arachidonic Acid-Derived Pro-Resolving Mediators Be a New Therapeutic Strategy for Asthma Therapy?

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Asthma represents one of the leading chronic diseases worldwide and causes a high global burden of death and disability. In asthmatic patients, the exacerbation and chronification of the inflammatory response are often related to a failure in the resolution phase of inflammation. We reviewed the role of the main arachidonic acid (AA) specialized pro-resolving mediators (SPMs) in the resolution of chronic lung inflammation of asthmatics. AA is metabolized by two classes of enzymes, cyclooxygenases (COX), which produce prostaglandins (PGs) and thromboxanes, and lypoxygenases (LOX), which form leukotrienes and lipoxins (LXs). In asthma, two primary pro-resolving derived mediators from COXs are PGE_2 and the cyclopentenone prostaglandin15-Deoxy-Delta-12,14-PGJ_2 (15d-PGJ_2) while from LOXs are the LXA_4 and LXB_4. In different models of asthma, PGE_2, 15d-PGJ_2, and LXs reduced lung inflammation and remodeling. Furthermore, these SPMs inhibited chemotaxis and function of several inflammatory cells involved in asthma pathogenesis, such as eosinophils, and presented an antiremodeling effect in airway epithelial, smooth muscle cells and fibroblasts *in vitro*. In addition, PGE_2, 15d-PGJ_2, and LXs are all able to induce macrophage reprogramming to an alternative M2 pro-resolving phenotype *in vitro* and *in vivo*. Although PGE_2 and LXA_4 showed some beneficial effects in asthmatic patients, there are limitations to their clinical use, since PGE_2 caused side effects, while LXA_4 presented low stability. Therefore, despite the strong evidence that these AA-derived SPMs induce resolution of both inflammatory response and tissue remodeling in asthma, safer and more stable analogs must be developed for further clinical investigation of their application in asthma treatment.

Keywords: asthma, lipoxins, PGE_2, 15d-PGJ_2, resolution

INTRODUCTION

Asthma is a high prevalence chronic inflammatory pulmonary disease, the respiratory symptoms of which include cough, wheezing, shortness of breath, and chest tightness which leads to elevated morbidity, mortality, and disease social and economic costs (1–3). Pulmonary inflammation is the hallmark of asthma, which is driven by a Th2 immune reponse to inhaled allergens, and associated with infiltration of the bronchial mucosa with eosinophils, CD4+ T cells, macrophages and, in exacerbations and severe cases, neutrophils (4, 5). Macrophages are classified into classical (M1) or alternative activation (M2a, M2b, M2c, or M2d subtypes). During allergic asthma, under exposure to Th2 cytokines (IL-4 and IL-13), macrophages are reprogrammed to M2a profile and perform diverse functions ranging between protective and pathogenic roles (6–9). Airway remodelling is another key feature of asthma pathogenesis and can precede the development of inflammation (10). It is characterized by mucous gland and airway smooth muscle (ASM) cells hyperplasia and/or hypertrophy, deposition of extracellular matrix (EM) proteins, and myofibroblast proliferation, leading to the thickening and occlusions of airways (11). In severe asthmatic patients, a failure in pro-resolving pathways extends the pro-inflammatory mechanisms, resulting in a chronic inflammation, which is associated with a major cause of admission to the intensive care unit and high mortality rates (12, 13). Lipid mediators, such as those originated by arachidonic acid (AA), are key factors of the resolution of inflammation, once they orchestrate the clearance of pro-inflammatory cells and signals promoting tissue restoration (13, 14). In this review, we discussed the impact of AA-derived specialized pro-resolving mediators (SPMs) in the resolution of inflammation and remodeling in asthma.

RESOLUTION OF INFLAMMATION

The resolution of inflammation is an active and controlled process that reduces inflammation through the elimination of danger signals, leading to the restoration of tissue homeostasis and preventing the progression towards an uncontrolled chronic inflammatory state. Thus, catabolization and antagonization of pro-inflammatory mediators, a decrease in leukocyte numbers at inflammatory sites, and tissue repair are key events in the resolution process (13). It is notewothy that different from classical anti-inflammatory molecules, the SPMs modulate the end of the inflammatory response, without promoting unwanted immunosuppression (15). During the resolution phase, leukocyte apoptosis and metabolization of

intracellular inflammatory signals lead to the clearance of inflammatory cells by specialized phagocytes. Together, these events promote the end of the acute inflammatory response and initiate tissue repair and healing (12, 16).

Endogenous mediators that actively participate in the resolution process include lipids (i.e., lipoxins, resolvins, maresin, and protectins), peptides (i.e. alpha-melanocortin-stimulating hormone and chemerin), proteins (i.e., annexin A1, Galectin-1, TGF-β and IL-10), and nucleotides (i.e. adenosine and inosine) (17–19). They promote cessation of polymorphonuclear infiltration into the inflamed tissue, reprogramming of macrophages and TCD4$^+$ cells to M2 and T regulatory phenotypes respectively, sequestration and counter-regulation of pro-inflammatory mediators, apoptosis of polymorphonuclear cells with subsequent phagocytosis by M2 macrophages, and tissue repair (20–22).

Among the SPMs, the lipid mediators activate many aspects of the resolution process (23). These endogenous mediators are biosynthesized in local inflamed tissue microenvironments, and can control the magnitude/duration of the inflammatory response as well as the timing of tissue restoration (17). They primarily come from the metabolism of polyunsaturated fatty acids, such as AA, docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), and docosapentaenoic acid (DPA) (15). Interestingly, several AA-derived mediators have consistently presented pro-resolving and tissue protecting activities in asthma (24, 25).

SPMs DERIVED FROM CYCLOOXYGENASES

Cyclooxygenases (COX), especially COX-2 isoform, play a pivotal role in the conversion of AA into different pro-inflammatory lipid mediators, including prostaglandins (PG) and thromboxanes (26). Despite the clear ligation of COX-2 activity with the development of the inflammatory response, it has also been proved that the inhibition of this enzyme impairs leukocyte clearance, indicating that some COX-2 derived mediators possess pro-resolving action. This occurs mainly due to the ability of COX-2 to metabolize EPA into resolvins, which are one of the main classes of SPMs (27). In asthma, beyond resolvins, the COX-2 activity also culminates in the formation of other important SPMs, such as PGE$_2$ and 15-Deoxy-Delta-12,14-PGJ$_2$ (15d-PGJ$_2$), a metabolite of PGD$_2$ (28).

PGE$_2$ is synthesized by three distinct enzymes, microsomal PGE synthase-1 (mPGES-1), mPGES-2, and cytosolic PGES (cPGES), which use PGH$_2$ as substrate. The actions of PGE$_2$ are mediated by four distinct 7TM receptors (EP1–EP4) (29). Although PGE$_2$ is a pro-inflammatory mediator, several works have shown that this lipid presents pro-resolving actions in some contexts (30). So, what determines when PGE$_2$ presents pro-resolving effects? There are three major factors, not mutually exclusive: i) time: the kinetics of PGE$_2$ release can separate its pro-inflammatory and pro-resolving effects due to the presence of different targets (31, 32); ii) context: eg. PGE$_2$ can inhibit ERK activation and MMP-1 secretion by gastric epithelial cells in the presence of cytokines, however, in their absence, PGE$_2$ does the opposite (31, 33, 34); iii) concentration: eg. very low PGE$_2$ concentrations inhibit chondrocyte-dependent

collagen cleavage in osteoarthritis cartilage, while higher concentrations enhance it (35).

IL-4 and IL-13, essential cytokines in the asthma pathogenesis (4), suppressed PGE_2 production by dendritic cells through reduction of COX-2 and mPGES-1 expression (36). Also, asthmatic patients presented an inverse correlation between the sputum levels of PGE_2 and eosinophil numbers (37, 38), suggesting that PGE_2 may reduce airway eosinophilia in these patients. Inhaled PGE_2 markedly inhibits the early and late bronchoconstrictor response to an allergen in asthmatic patients (39); however, these effects may be related only to the PGE_2-induced ASM relaxation (40). Nevertheless, COX-1 knock out (KO) and EP2KO mice that were ovalbumin (OVA)-sensitized and challenged showed increased eosinophilia and Th2 cytokines levels in the lungs and bronchoalveolar lavage (BAL), respectively, compared to wild-type (WT) mice (41, 42). Besides, treatment with PGE_2 inhibited the house dust mite (HDM)-induced lung eosinophilia (43), and OVA-provoked accumulation of eosinophils and Th2 cytokines in the BAL (42), probably because PGE_2 can inhibit $β_2$ integrin and L-selectin function with a consequent reduction in eosinophil migration (44, 45). Furthermore, prior studies of our group showed that PGE_2 derived from eosinophils induced an early resolution of allergic pleural edema (25, 46).

Until now, there has been no agreement on the effects of PGE_2 on the differentiation of naïve T cells to Th1, Th2, or Th17 (47); however, type 2 innate lymphoid cells (ILC2), that emerged in the literature as novel Th2 cytokine-producing cells, strongly express both EP2 and EP4. PGE_2 inhibited proliferation, activation, and release of cytokines by ILC2 (48, 49). Besides, alveolar macrophages from asthmatics presented a reduction in the EP2 expression (50) and PGE_2 generation, in parallel with decreased efferocytosis of apoptotic cells (51). PGE_2 is a well-known inductor of M2 macrophage reprogramming (52). Furthermore, PGE_2 induced IL-10 production by macrophages *in vitro*, and the adoptive transfer of those PGE_2-treated macrophages led to fewer infiltrating eosinophils, macrophages, activated TCD4+, and regulatory T lymphocytes in lungs of HDM-exposed mice (43).

In lung fibroblasts, there is an inverse relationship between COX-2 and mPGES-1 expression and the number of allergen challenges, resulting in a reduction in PGE_2 production by those cells (53). Besides, mPGES-1 KO mice showed an augmentation of allergen-induced vascular smooth muscle cell numbers and thickness of intrapulmonary vessels (54). PGE_2 also inhibited fibroblast migration, proliferation, collagen deposition, and myofibroblast differentiation in the lung (55). *In vitro*, PGE_2 decreased the expression of tenacin C and fibronectin by human fibroblast and ASM cells (56), reduced the proliferation of ASM cells derived from asthmatic patients (57), and upregulated the expression of the anti-inflammatory protein tristetraprolin in human ASM cells (58). Prior investigations of our group revealed that the instillation of glucagon induced a high production of PGE_2 into the lungs (59). Also, we reported that a non-selective COX inhibitor decreased the inhibitory effect of glucagon on OVA-induced collagen deposition in the lungs (60), suggesting that the anti-remodeling effect of glucagon depends on PGE_2 production. Interestingly, inhaled PGE_2 showed bronchodilator capacity in small clinical trials with asthmatic patients (61, 62) (**Table 1**).

Despite the possible benefits of PGE_2 in asthma, non-selective COX inhibitors improved specific airway conductance and airway constriction of asthmatics (63, 64), suggesting that COX-derivatives may play a role in the development or worsening of asthma. Nevertheless, patients with mild allergic asthma treated with specific COX-2 inhibitors did not present an effect on lung function and eosinophil accumulation in the sputum (65) (**Table 1**). Although PGE_2 acts directly in the resolution of inflammation, it can also drive a pro-inflammatory response in human fibroblast and ASM cells (56). Furthermore, PGE_2 apparently desensitized β2 adrenergic receptors during asthma exacerbation triggered by

TABLE 1 | Summary of clinical studies using mediators related to arachidonic acid metabolism pathways in asthma.

Drug	Classification	Key Results	Side Effects	Ref.
PGE_2	PGE_2	Inhalation of PGE_2 inhibited the early and late bronchoconstriction response to inhaled allergen in asthmatic patients	Cough and retrosternal soreness transient	(39)
PGE_2	PGE_2	Inhalation of PGE_2 reduced exercise-induced bronchoconstriction in asthmatic patients	Cough and retrosternal soreness transient	(61)
PGE_2	PGE_2	Aerosolization of PGE_2 had a bronchodilator effect in patients with bronchial asthma	Headache, cough and irritation of the pharynx	(62)
Indomethacin	COX inhibitor	Oral administration of Indomethacin induced a slight decrease in allergy sensitivity measured by specific airway conductance in asthmatic patients	No side effects were evaluated	(63)
Indomethacin	COX inhibitor	Inhalation of Indomethacin reduced exercise-induced bronchoconstriction in asthmatic children	No side effects were evaluated	(64)
Etoricoxib	COX-2 inhibitor	Etoricoxib had no effect on allergen-induced airflow obstruction and sputum eosinophils, basal lung function, or methacholine responsiveness in mild asthma patients	No side effects were observed	(65)
Pioglitazone	PPAR-γ agonist	Pioglitazone had no effect on symptoms, airflow obstruction and inflammation in patients with severe asthma	Peripheral edema and presumptive angioedema	(66)
LXA_4	LXA_4	Nebulization of LXA_4 inhibited LTC4-induced airway obstruction in asthmatic patients	No side effects were observed	(67)
5(S),6(R)-LXA_4 methyl ester	LXA_4 analog	Inhalation of 5(S),6(R)-LXA_4 methyl ester improved pulmonary function in asthmatic children with acute episodes	No side effects were observed	(68)
BML-111	LXA_4 receptor agonist	Inhalation of BML-111 improved pulmonary function in asthmatic children with acute episodes	No side effects were observed	(68)

COX, Cyclooxygenase; LXA_4, Lipoxin A_4; PGE_2, Prostaglandin E_2; PPAR-γ, Peroxisome proliferator-activated receptor; Ref, References.

Rhinovirus infection (69). A high dose of PGE_2 can also induce airway contraction in asthmatic patients, probably through activating different receptors (70), and cough by activation of EP3 receptor (71). As the most of pro-resolving actions of PGE_2 are related to the activation of EP2, the development of selective agonists of this receptor can be a good strategy to be consider for treating asthma in the future.

$15d-PGJ_2$ is formed spontaneously by a series of dehydration of PGD_2 (72), and it is produced abundantly in the inflamed site, making it important in the resolution of the inflammation (73). Most of the pro-resolving actions of $15d-PGJ_2$ depend on the peroxisome proliferator-activated receptor-gamma (PPARγ) activation, but some of its effects are independent of this receptor (74). In asthmatic patients, there is a reduction in the PPARγ expression in BAL cells (75). Furthermore, polymorphism of the PPARG gene may be related to an increased risk of asthma development (76). Activation of PPARγ by synthetic agonists reduced the levels of Th2 cytokines and inhibited AHR, the influx of eosinophils and structural changes in the airway wall in murine OVA-challenge models of asthma (77, 78). Together, these data indicate that the reduction in PPARγ expression by inflammatory cells in asthmatic patients may be one of the mechanisms that contribute to the development of chronic asthma.

In a model of carrageenin-induced pleurisy, 48h after the provocation, when mononuclear cells dominate the reaction up to the resolution, there was an immense increase in COX-2 protein expression and $15d-PGJ_2$ levels coincident with inflammatory resolution and associated with minimal exudate PGE_2 levels. In this model, the use of both nonselective or selective COX-2 inhibitors, 24h after carrageenin challenge, increased the number of inflammatory cells and exudate volume in parallel to a reduction in the $15d-PGJ_2$ levels. In addition, $15d-PGJ_2$ reversed the selective-COX-2 inhibitor-induced rise in cell number and exudate volume, indicating that the production of $15d-PGJ_2$ is important to the resolution in this model (79). The pro-resolving effect of $15d-PGJ_2$ was related to an induction of apoptosis of inflammatory cells (80). Besides, $15d-PGJ_2$ also regulates the balance of cytokines and chemokines that control leukocyte trafficking during acute inflammation, promotes M2 macrophage differentiation, as well as the efflux of macrophage to draining lymphatics, facilitating the resolution of inflammation (81). This pro-resolving effect of $15d-PGJ_2$ may be dependent on PPARγ, once IL-4-induced PPARγ activity becomes indispensible for M2 activation (82, 83).

In an OVA-induced asthma model, KO mice for PGD synthase (H-PGDS), an enzyme that catalyzes PGH_2 into PGD_2, showed accelerated chronic allergic lung eosinophil inflammation in parallel to an increase in the local levels of TNFα and eotaxin-1. Furthermore, the exogenous administration of $15d-PGJ_2$ decreased the excessive eosinophilic infiltration and TNFα and eotaxin-1 levels noted in those mice (84). Furthermore, the activation of PPARγ reduced OVA-induced eosinophilia and IL-4, IL-5, and IL-6 levels in the lungs of mice (85). We previously showed that interventional treatment with $15d-PGJ_2$ inhibited both OVA- and HDM-induced eosinophils accumulation and IL-5 and IL-13 levels in the lungs (86). The pro-resolving effect of $15d-PGJ_2$ on lung eosinophilia is probably related to its ability to block the traffic and induce apoptosis of these

granulocytes (87). The inhibitory effect of $15d-PGJ_2$ on eosinophil migration is possibly dependent on PPARγ, once the activation of this receptor by synthetic agonists inhibits chemotaxis of eosinophils (85). However, the pro-apoptotic effect of $15d-PGJ_2$ is independent of PPARγ (87). $15d-PGJ_2$ also inhibited T lymphocyte proliferation in a mechanism probably dependent on PPARγ, as it is mimicked by PPARγ synthetic agonists (88, 89).

We previously demonstrated that interventional treatment with $15d-PGJ_2$ reversed structural changes related to airway remodeling, including epithelial thickening, mucus exacerbation, and EM deposition, in both OVA and HDM murine models of asthma (86). These antiremodeling effects of $15d-PGJ_2$ may be related to its ability to reduce differentiation of fibroblasts into myofibroblasts, the proliferation of myofibroblasts (90), and fibroblast growth factor-induced human ASM cell proliferation (91). Although PPARγ agonists are extremely promising to asthma therapy, unfortunately severe asthmatic patients treated with pioglitazone did not present with an improvement in asthma features and showed significant side effects (66) (**Table 1**).

SPMs DERIVED FROM LIPOXYGENASES

5- Lipoxygenase (LOX) and 15-LOX are the main LOXs involved in the metabolization of AA (92), resulting in the formation leukotrienes (LTs) and lipoxins (LXs). While LTs are recognized to exert broad proinflammatory effects, LXs present pro-resolving actions (93). Endogenously, LXs are typically produced by three main pathways. In one route, LXA_4 and LXB_4 are produced by 5-LOX (94), and in other by 12-LOX (95). It is described that aspirin treatment can also promote the synthesis of LXs epimers denominated aspirin-triggered lipoxins (ATLs), including 15-epimeric (epi)-LXA_4 and 15-epi-LXB_4 (94). LXA_4 and ATLs act primarily on a 7TMN receptor denominated ALXR (96). ALXR is expressed in several tissues, including lungs, and different cell types such as leukocytes, fibroblasts, and bronchial epithelial cells. LXA_4 can also activate the aryl hydrocarbon receptor, and both LXA_4 and ATLs are antagonists of the cysteinyl leukotriene receptor 1 (97). Nevertheless, the LXB_4 receptor has not yet been identified (98).

The failure in the generation and action of LXs is associated with more severe airway inflammation (99). Indeed, severely asthmatic patients presented a reduction of LXA_4 levels in BAL fluid, sputum, and whole blood compared to moderately asthmatic individuals. This reduction in LXA_4 concentrations observed in severe asthma was associated with a higher degree of airway obstruction (24). Eosinophils from the blood of asthmatic patients presented a decreased ALXR expression compared to those obtained from healthy individuals (100). Furthermore, transgenic mice that overexpress ALXR showed a reduction in OVA-induced eosinophilia in the BAL and lung tissue (101). We previously showed that 15-epi-LXA_4 analogs inhibited OVA-induced pleural eosinophil influx by reducing local eotaxin and IL-5 generation (102). We also noted that 15-epi-LXA_4 analogs accelerate the drainage of OVA-induced pleural edema (25). In human eosinophils, LXA_4 inhibited chemotaxis toward chemoattractants (103), and granulocyte-macrophage colony-stimulating factor-

induced IL-13 and eotaxin release *in vitro* (104). In spite of inhibiting eosinophil migration, 15-epi-LXA$_4$ is a potent chemoattractant to monocytes *in vitro* (105) and restored the balance between M2 and M1 populations into the lungs in a murine model of pulmonary damage induced by bleomycin (106). Furthermore, LXA$_4$ stimulates macrophage efferocytosis of apoptotic polymorphonuclear cells and cellular debris (107).

Among the ILC family, natural killer (NK) cells and ILC2s are important in the control and exacerbation of asthma, respectively. NK cell depletion induced a persistent allergic airway inflammation in association with reduction of the LXA$_4$ levels in the BAL (108). LXA$_4$ enhanced activated NK cells-induced eosinophil apoptosis through ALXR activation (109). Meanwhile, the blood and sputum of patients with severe asthma presented elevated numbers of ILC2 compared to mild asthmatics, which was related to persistent airway eosinophilia (110). LXA$_4$ inhibited both PGD$_2$- and IL-25 plus IL-33-induced IL-13 release by ILC2 *in vitro* in a mechanism dependent on ALXR activation (109).

In vitro, LXA$_4$ and 15-epi-LXA$_4$ reduced IL-8 secretion induced by serum amyloid A in a human alveolar A549 cell line (111). Also, activation of ALXR by LXA$_4$ increased basal proliferation and wound repair of human airway epithelial cells (112). In a murine model of asthma caused by OVA, airway epithelial cells presented with an increased expression of ALXR (101) and LXB$_4$ reduced mucus production (113). ASM hypertrophy and hyperplasia, as well as accumulation of muscle cells in the subepithelial layer, are some of the changes observed in asthma remodeling. It was shown that LXA$_4$ reduced both LTE$_4$- and IL-13–primed ASM migration toward platelet-derived growth factor *in vitro* (114). Another critical pathological feature of airway remodeling in asthma is the EM deposition in the peribronchiolar area. It is noteworthy that both fibroblasts and myofibroblasts can express ALXR (115). Moreover, LXA$_4$ inhibited connective tissue growth factor-induced human lung fibroblast proliferation *in vitro* (115) and blocked TGF-β-triggered increase in α-smooth muscle actin expression and collagen release by human myofibroblasts *in vitro* (116). Besides, treatment with 15-epi-LXA$_4$ reversed bleomycin-promoted fibrosis and lung damage in mice (106). Altogether, these data suggest a potential role of LXs in the resolution of the airway and peribronchiolar remodeling observed in asthmatics.

Due to the possible therapeutic application of LXA$_4$, some clinical trials using this LX, its analogues, or LXA$_4$ receptor agonist BML-111 were administered in asthmatic patients. The nebulization of LXA$_4$ reduced LTC4-induced bronchoconstriction (67); however, the rapid inactivation and significant instability to exposure to light and acids of LXA$_4$ (117) make its clinical use difficult. Furthermore, the inhalation of LXA$_4$ analog or BML-111, which is more potent and stable than LXA$_4$ itself (118), improved the lung function (68) (**Table 1**). Interestingly, both LXA$_4$ analog and BML-111 were well tolerated and presented no side effects (68).
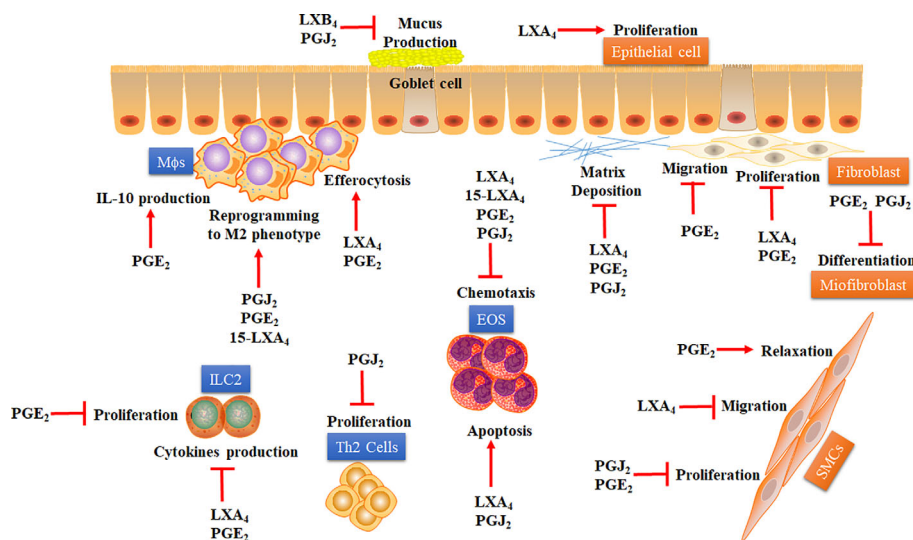
FIGURE 1 | Proposed mechanisms whereby COX- and LOX-derived lipid mediators may accelerate the resolution of lung inflammation in asthma. Some COX- and LOX-derived lipid mediators, including PGE$_2$, 15dPGJ2, LXA$_4$, and LXB$_4$, have demonstrated several pro-resolving actions over immune cells (blue squares) and structural cells (orange squares) involved in asthma. Pro-resolving effects of COX- and LOX-derived lipid mediators are: i) inhibition of EOS chemotaxis and stimulation of apoptosis on those cells; ii) inhibition of ILC-2 proliferation and cytokine production; iii) inhibition of Th2 lymphocytes proliferation; iv) stimulation of efferocytosis and IL-10 production by MΦs; v) induction of macrophage reprogramming to alternative M2 phenotype. Besides, these SPMs derived from COX and LOX present some important antiremodeling effects in asthma, like: i) inhibition of mucus production by globet cells and stimulation of airway epithelial cells proliferation; ii) inhibition of proliferation and migration of SMCs and stimulation of relaxation of these cells; iii) inhibition of proliferation, migration, and extracellular matrix deposition by fibroblasts; iv) inhibition of fibroblast differentiation into myofibroblasts. EOS: Eosinophil. ILC-2: Type-2 innate lymphoid cells. LXA$_4$: Lipoxin A$_4$. 15-LXA$_4$: 15-epimeric (epi)-LXA$_4$. LXB$_4$: Lipoxin B$_4$. MΦs: Macrophages. M2: M2 macrophage phenotype. PGE$_2$: Prostaglandin E$_2$. PGJ$_2$: 15-Deoxy-Delta-12,14-PGJ$_2$. SMCs: Smooth muscle cells. Th2: Type-2 CD4+ T helper. The arrow represents stimulation while the flat arrow represents inhibition.

CONCLUSION

This mini-review presents several aspects of the pro-resolving effects of COX- and LOX-derivative mediators in asthma (**Figure 1**), addressing their efficacy and current limitations for clinical use. Nevertheless, the review presents several strong pieces of evidence that support the development of new drugs based on analogs of PGE_2, 15d-PGJ_2, and LXs with better physical-chemical properties, allowing greater stability and superior selectivity for specific receptors. Moreover, new analogs of AA-derived SPMs could also improve efficiency and reduce the required dose of glucocorticoid, the latter often leading to adverse effects and steroid-refractoriness, despite being the best asthma treatment so far.

AUTHOR CONTRIBUTIONS

DI, MF, and DC contributed to the conception and design of the study, wrote the manuscript, discussed the content, and contributed to the manuscript revision. MM discussed the content and contributed to the manuscript revision. VC contributed to the conception and design of the study, wrote the manuscript, discussed the content, and contributed to the manuscript revision. All authors reviewed and/or edited the manuscript prior submission. All authors contributed to the article and approved the submitted version.

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