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Invited review article

Role of omega-3 fatty acids and their metabolites in asthma and allergic diseases

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Abbreviations:
BALF, bronchial alveolar lavage fluid; COX, cyclooxygenase; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; HETE, hydroxyeicosatetraenoic acid; HEPE, hydroxyeicosapentaenoic acid; IL, interleukin; LC, liquid chromatography; LOX, lipoxygenase; LT, leukotriene; LX, lipoxin; MS/MS, tandem mass spectrometry; PD1, protectin D1; PG, prostaglandin; Rv, resolvin; SPM, specialized pro-resolving mediator; SPT, skin prick test

ABSTRACT

Omega-3 fatty acids, docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), are found naturally in fish oil and are commonly thought to be anti-inflammatory nutrients, with protective effects in inflammatory diseases including asthma and allergies. The mechanisms of these effects remain mostly unknown but are of great interest for their potential therapeutic applications. Large numbers of epidemiological and observational studies investigating the effect of fish intake or omega-3 fatty acid supplementation during pregnancy, lactation, infancy, childhood, and adulthood on asthmatic and allergic outcomes have been conducted. They mostly indicate protective effects and suggest a causal relationship between decreased intake of fish oil in modernized diets and an increasing number of individuals with asthma or other allergic diseases. Specialized pro-resolving mediators (SPM: protectins, resolvins, and maresins) are generated from omega-3 fatty acids such as EPA and DHA via several enzymatic reactions. These mediators counter-regulate airway eosinophilic inflammation and promote the resolution of inflammation *in vivo*. Several reports have indicated that the biosynthesis of SPM is impaired, especially in severe asthma, which suggests that chronic inflammation in the lung might result from a resolution defect. This article focuses on the beneficial aspects of omega-3 fatty acids and offers recent insights into their bioactive metabolites including resolvins and protectins.

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Introduction

Omega-3 fatty acids, docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), are polyunsaturated fatty acids found mainly in fish oil. Epidemiological studies have shown that these compounds play protective roles in cardiovascular diseases such as myocardial or cerebral infarction, hypertension, and hyperlipidemia.[1] Also, there is a growing evidence that omega-3 fatty acids have beneficial effects in chronic inflammatory diseases including chronic obstructive pulmonary disease (COPD), asthma, rheumatoid arthritis, and inflammatory bowel disease.[2,3] In addition, it is thought that atopic sensitization and allergic outcomes also can be prevented by fish intake during pregnancy, infancy, and childhood.[4,5] Contemporary changes in diet resulting in a lower omega-3:omega-6 fatty acid ratio might contribute to exacerbation and increased morbidity of asthma and allergic diseases.

Prostaglandins and leukotrienes are arachidonic acid-derived lipid mediators converted via cyclooxygenase and lipoxygenase, respectively. Prostaglandin D2 and cysteinyl leukotrienes, produced mainly by mast cells and eosinophils, function as potent bronchoconstrictors and pro-inflammatory molecules in allergic airway

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inflammation.[6,7] Recent biochemical studies showed that omega-3 fatty acids such as DHA and EPA function as precursors for bioactive molecules called resolvins, protectins, and maresins.[8,9] Currently, leukotriene and prostaglandin receptor antagonists are the newest drugs available for the treatment of asthma, but basic research findings now indicate that pro-resolving lipid mediators are potentially the next therapeutic targets for allergic diseases.

Asthma is a common respiratory disease affecting 300 million people worldwide.[10] Inhaled corticosteroids are an established treatment, but 5–10% of asthma patients are resistant to this therapy, leading to difficulties in managing the disease.[11] Leukotriene receptor antagonists are widely used as another first-line therapeutic agent in asthma, suggesting that abnormal lipid metabolism contributes to disease pathophysiology. Recently, several reports have indicated that biosynthesis of anti-inflammatory and pro-resolving lipid mediators, lipoxin A4 (LXA4) or protectin D1 (PD1), are dysregulated in severe asthma,[12–21] suggesting that an imbalance between pro- and anti-inflammatory molecules causes the exacerbation of inflammation observed in airways of asthmatic patients.

Epidemiological/clinical studies of omega-3 fatty acids in asthma and allergic diseases

A large epidemiological study in Greenland showed that intake of omega-3 fatty acids was inversely associated with asthma morbidity. Since then, many epidemiological and clinical studies focusing on omega-3 fatty acid intake or supplements have been conducted. For example, the concept underlying these studies is supported by the finding that the DHA content compared with arachidonic acid in nasal tissues from patients with asthma was lower than in healthy subjects,[22] which suggests a possible protective role of DHA in allergic diseases. Thus, it has been of great interest for some time whether long-chain omega-3 fatty acids or their natural sources, fish or fish oils, have beneficial effects on asthma or other allergic outcomes.

Many epidemiological studies of maternal fish intake during pregnancy have shown beneficial effects on allergic or atopic outcomes in infants or children of those pregnancies.[23–27] In addition, the majority of reports investigating fish intake during infancy or childhood have suggested a protective role in allergic outcomes.[28–36] These allergic or atopic outcomes included incidence of atopic diseases or symptoms (asthma, wheezing, eczema, and hay fever), food sensitization, and prevalence of positive skin prick test (SPT). One study of fish intake during lactation demonstrated that higher levels of EPA in breast milk correlated with a lower risk of atopic dermatitis.[37] On the other hand, observational studies in adults have been inconsistent in showing benefits in asthma of fish or fish oil intake.[38–45] However, several reports indicated that omega-3 fatty acid intake lower asthma incidence, prevalence of asthma-related symptoms, or exhaled nitric oxide (NO) levels and improve lung functions in adults.[38,40–43] An epidemiological survey of young adult Americans revealed that high intake of omega-3 fatty acids, especially DHA compared with EPA, prevented asthma onset.[43] These findings raise the possibility that omega-3 fatty acids are useful in the prevention of adult-onset asthma. Another study also demonstrated superiority of DHA compared to other fatty acids in terms of improved lung function.[42] A relationship between low omega-3 fatty acid intake and increased respiratory symptoms (chronic bronchitis, wheeze, and asthma) was shown in another study,[40] suggesting beneficial effects of omega-3 fatty acids in the lung.

Clinical trials using fish oil supplementation during pregnancy and lactation revealed that maternal intake of fish oil resulted in higher levels of omega-3 fatty acids in the offspring,[46–51] along with anti-inflammatory changes in immunological parameters (cytokine production, lipid mediator release, and cellular populations).[51–57] These studies also suggested that fish oil supplementation reduced the prevalence and severity of atopic dermatitis and food sensitization in the first year of life, and that these beneficial effects might persist until adolescence, with a reduced incidence of eczema, hay fever, and asthma.[53,58,59] Fish oil supplementation in infants and children increased the concentrations of those fatty acids in plasma[60–64] and blood cells[65] and had modulatory effects on the immune systems of infants[65] and children.[61,66] Clinical intervention with fish oil supplements in infants/children from 6 months old to 5 years old showed that there was a decreased prevalence of wheeze and lower bronchodilator use at 18 months of age,[63,67] and reduced allergic sensitization and prevalence of cough at 3 years of age, but without effects on asthma prevalence.[64] Two studies examined whether fish oil supplements have beneficial effects on asthmatic symptoms and lung function in patients with asthma in children,[61,68] but in only one study did intervention significantly reduce asthma severity and improve lung functions.[68] The data obtained from clinical trials of fish oil and omega-3 fatty acid supplements in adult asthma are inconsistent. However, several studies demonstrated protective effects of omega-3 fatty acid supplementation in adult asthmatic patients.[69–72] Mickleborough et al., showed that intake of omega-3 fatty acid supplements reduced bronchoconstriction after exercise accompanied by lower production of leukotrienes from polymorphonuclear cells in athletes[71] and adult patients with asthma.[70] Two other reports demonstrated the beneficial and suppressive effects of omega-3-rich supplementation on exhaled NO levels before and after allergen challenge, serum eosinophil counts, eosinophilic cationic protein levels, and *in vitro* cysteinyl leukotriene release,[72] or daytime wheeze, exhaled H_2O_2 levels, and morning PEF, respectively.[69] Various factors, e.g., types of oils, doses, duration, and quality or purity of fish oil or omega-3 fatty acid supplements were inconsistent among clinical studies. Characteristics of the subjects in these studies were also different (age, smoking history, country of origin, medication, etc.). There is clearly much room for improvement in study design and protocols to obtain more easily interpretable information.

Omega-3 fatty acids or their metabolites in murine asthma models

To investigate potential beneficial effects of omega-3 fatty acids in asthma, it is of interest to determine whether administration or elevated levels of omega-3 fatty acids can suppress eosinophilic inflammation *in vivo*. Several reports have indicated that omega-3 fatty acids function as protective molecules in murine models of asthma,[73–76] although those regulatory functions were not observed in other studies.[77,78] DHA inhalation during the allergen challenge phase in mice suppressed airway eosinophilic inflammation, and this was accompanied by reduced numbers of inflammatory cells in bronchoalveolar lavage fluid (BALF) and decreased airway hyperresponsiveness, and mucus production.[76] Morin et al., developed a new monoglyceride DHA derivative (CRBM-0244)[74] and EPA derivative (EPA-MAG)[75] and showed their preventive effects on airway eosinophilic inflammation, airway hyperresponsiveness and inflammatory cytokine production in OVA-induced asthmatic responses.

Fat-1 is a *C. elegans* enzyme that converts omega-6 fatty acids into omega-3 fatty acids. Fat-1 transgenic mice (Fat-1 mice) have been established and used as an experimental model to determine if higher ratios of omega-3 fatty acids to omega-6 fatty acids can contribute to anti-inflammatory responses in various conditions. In experiments using these mice, substantial amounts of omega-3

fatty acids are detected at steady state baseline in the lung. In a murine model of asthma using OVA, the number of inflammatory cells in BALF, mucus production, airway hyperresponsiveness, and Th2 cytokine concentrations (IL-5, IL-13) were decreased in the fat-1 transgenic mice. Lipidomic analysis demonstrated that the levels of pro-resolving lipid mediators, PD1 and resolvin E1 (RvE1), which are synthesized in lung, were significantly increased in inflamed lungs of fat-1 transgenic mice.[73]

Pro-resolving lipid mediator (Protectins Resolvins Maresins)

Biosynthesis and cell sources of protectins and resolvins

Lipidomic analysis of murine inflammatory exudates or activated cell supernatant identified specific pro-resolving lipid mediators, including protectins, resolvins, and maresins, synthesized from omega-3 fatty acids during the resolution phase. These molecules are generally termed specialized pro-resolving mediators (SPM).[8,9,79] Protectins and Resolvin D-series lipid mediators are produced by 15-lipoxygenase in human and 12/15-lipoxygenase in mouse. These enzymes convert DHA to 17-hydro(peroxy)docosapentaenoic acid (17-HpDHA), a compound that is further metabolized into protectins and resolvin Ds. Resolvin E series are produced via the acetylated cyclooxygenase-2 or cytochrome P450 pathways. These enzymes convert EPA to 18-hydroxyeicosapentaenoic acid (18-HEPE), which is further metabolized into resolvin Es (Fig. 1).

15-lipoxygenase or 12/15-lipoxygenase are expressed in Th2 cytokine-stimulated monocyte or macrophages, retinal epithelial cells, microglial cells, and airway epithelial cells. In addition, we demonstrated that human and murine eosinophils highly expressing 15-lipoxygenase-1 or 12/15-lipoxygenase have the capacity to produce PD1.[21,80] We also identified 12/15-lipoxygenase-dependant anti-inflammatory lipid mediators, resolvin E3 and 12-hydroxy-17,18-epoxyeicosatetraenoic acid.[81–83]

Cyclooxygenase-2 and cytochrome P450 are expressed in neutrophils, macrophages, epithelial cells, and other structural cells.

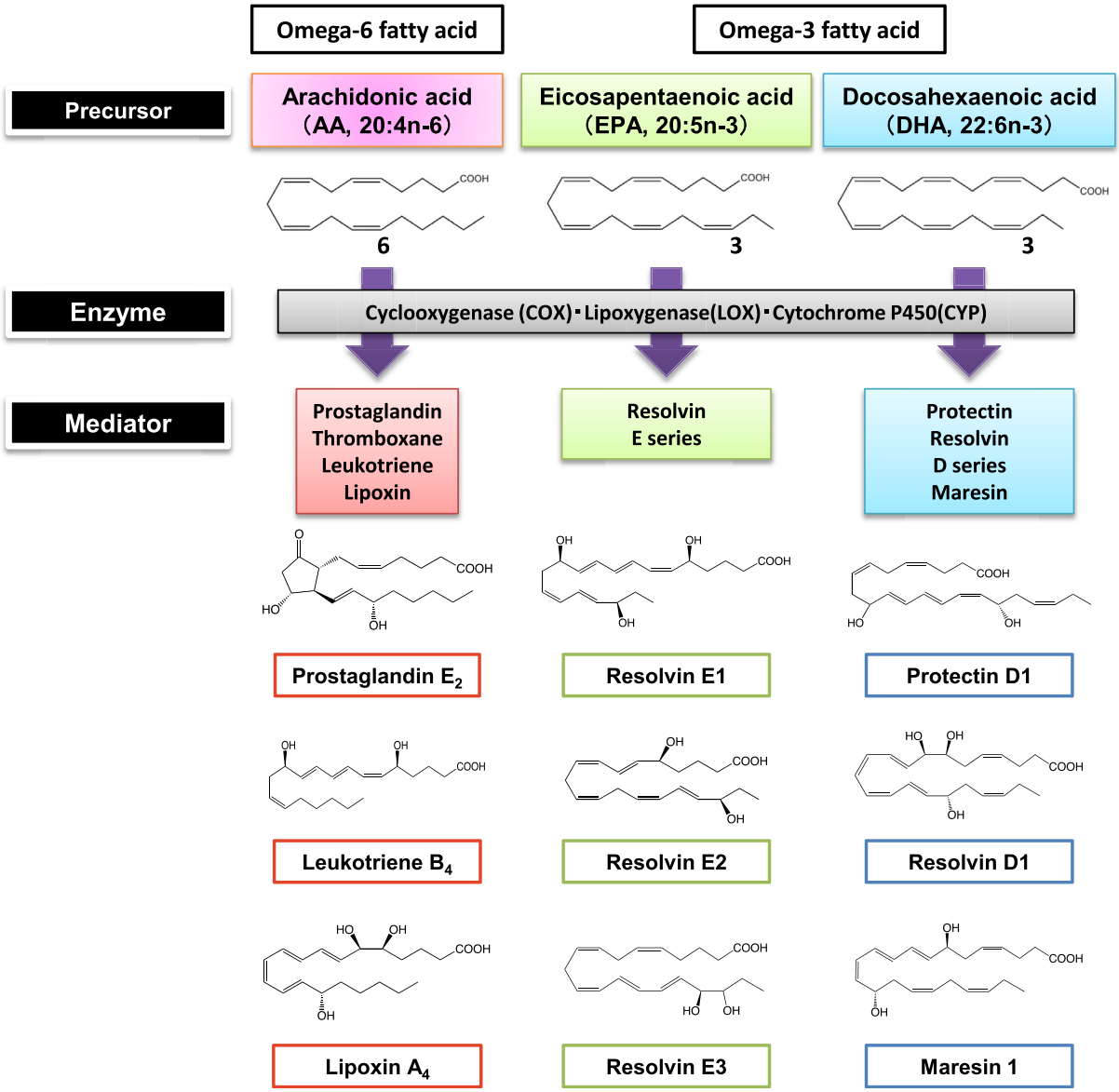

Fig. 1. Polyunsaturated fatty acid-derived lipid mediators. Arachidonic acid is a metabolic precursor to eicosanoids (i.e. prostaglandins and leukotrienes) that have distinct roles as pro-inflammatory mediators. In contrast, omega-3 fatty acids are converted to bioactive metabolites such as resolvins and protectins with anti-inflammatory and pro-resolving properties.

COX-2 is induced by stimulatory signals in various cells types and can modify inflammatory responses thorough its major metabolites, the prostaglandins. Cell–cell interactions between cells expressing different enzymes are also necessary for the biosynthesis of these mediators.[84]

Receptors and biological functions

The search for receptors specific to the newly discovered lipid mediators – protectins, resolvins, and maresins – is now underway, and some receptors with high affinity for resolvin D1 (RvD1), D3, D5 and RvE1 have been identified. However, the receptor specific for PD1 remains unknown, although its existence on neutrophils, pigment epithelial cells, and neuronal cells have been suggested.[85,86] Two high affinity receptors for RvD1 and LXA4, namely ALX (FPR2, FPRL1) and GPR32, were identified.[87] GPR32 is also responsive to RvD3 and RvD5.[88,89] RvE1, an EPA-derived lipid mediator, binds to ChemR23, a receptor for chemerin, and antagonizes BLT1, a receptor for LTB4.[90–92] These mediators possess proresolving functions as inhibitors of neutrophil accumulation into inflammatory sites and promoters of apoptotic cell clearance by macrophages.[93] Many types of inflammatory cells, including eosinophil, mast cells, T cells, and dendritic cells, are also directly regulated by these mediators.

Pharmacological effects in a murine models of asthma (Table 1)

(A) Protectin D1 (PD1)

In a murine model of asthma using ovoalbumin (OVA), intravenous administration of PD1 decreased the number of inflammatory cells in BALF and inhibited airway hyperresponsiveness and mucus production, suggesting protective effects on asthmatic responses *in vivo* without changes of IL-5 concentration in BALF.[94] TLR7 is necessary for the recognition of single stranded RNA of respiratory viruses. TLR7 agonists had preventive effects on allergic airway inflammation *in vivo* in mice[95–97] and functioned as bronchodilators in humans, indicating that they are potential therapeutic targets in asthma. Interestingly, TLR7 signaling promotes the resolution of airway eosinophilic inflammation through upregulation of 12/15-lipoxygenase metabolism, and its metabolites such as PD1 and RvD1 also showed suppressive effects.[98]

(B) Resolvin D1 (RvD1)

Intravenous administration of RvD1 inhibited airway eosinophil accumulation and mucus production with decreased IL-5 production in a murine model of asthma. *In vitro*, RvD1 promoted phagocytosis by alveolar macrophages, suggesting that RvD1 enhances the clearance of apoptotic inflammatory cells in the airway. Administration of RvD1 during the resolution phase also dampened eosinophilic inflammation.[99,100] As mentioned in the PD1 section, RvD1 promoted the resolution of airway eosinophilic inflammation and its biosynthesis was induced in part thorough the TLR7 cascade.[98]

(C) Resolvin E1 (RvE1)

Various reports have demonstrated the protective effects of RvE1 on airway eosinophilic inflammation *in vivo*.[101–104] In an OVA-induced murine asthmatic model, intraperitoneal administration of RvE1 during the sensitization phase, challenge phase, or both inhibited the production of OVA-specific IgE, inflammatory cell accumulation in the airways, airway hyperresponsiveness, mucus production, and Th2 cytokine (IL-5, IL-13) production.[101,102] In addition, intravenous administration of RvE1 during the resolution phase also dampened inflammatory cell accumulation in the airways, airway hyperresponsiveness, and mucus production. These effects were mediated by the inhibition of Th17 cytokines (IL-17A IL-23 IL-6) and the increased production of IFN-γ with no differences in Th2 cytokines (IL-5· IL-13) between vehicle and RvE1 treated groups.[104] In this setting, RvE1 directly modulated cytokine production by dendritic cells and activated natural killer (NK) cells,[103] the main producers of IFN-γ and active inducers of eosinophil apoptosis.[105] RvE1 binds to ChemR23, also known as the chemerin receptor. Recently, a new membrane-anchored chemerin receptor agonist was discovered and pharmacological assessment using a murine model of allergic airway inflammation revealed its immunomodulatory functions.[106]

Biosynthesis in human asthma (Table 2)

(A) Protectin D1(PD1)

The presence of PD1 in the airways of normal human subjects has been documented in condensates of exhaled breath, with a decrease in PD1 levels below the detection limit in exhaled breath condensates of asthmatic patients during exacerbation of the disease.[94] We found decreased productions of PD1 and 15-HETE, a 15-lipoxygenase metabolite of arachidonic acid, by stimulated peripheral blood eosinophils from patients with severe asthma, suggesting an impairment in 15-lipoxygenase activity in severe asthma.[21] In contrast, the similar levels of 5-HETE, a 5-lipoxygenase product of arachidonic acid, were observed in patients with severe asthma and healthy subjects, indicating a selectively dysregulated enzymatic activity of 15-lipoxygenase[21] (Fig. 2).

Table 1
Pharmacological effects of SPM in murine models of asthma.

SPM	Administration	Timing			Inflammatory cell (BALF)	Cytokines, lipid mediators	AHR	Mucin	Reference
		Sensitization	Challenge	Resolution					
PD1	I.V.		○	○	EOS↓ LYM↓	IL-5 → IL-13↓ PGD2↓ cysLTs↓	↓	↓	94
RvD1	I.V., I.N.		○	○	EOS↓ LYM↓ MΦ↑	IL-4 → IL-5↓ IL-10 → IL-13 → IL-17↓ IL-23↓CCL11 → CCL17→ IFN-γ → LTB4↓ LXA4→	↓	↓	100
RvE1	I.P.	○	○		EOS↓ LYM↓	IL-4↓ IL-5↓ IL-13↓ CCL5↓ IgE↓	↓	↓	101,102
RvE1	I.V.		○	○	EOS↓ LYM↓ NK↑	IL-4 → IL-5 → IL-13 → IL-6↓ IL-17↓ IL-23↓ IL-27↓ IFN-γ↑ LTB4↓cysLTs → LXA4↑	↓	↓	103,104
LXA4	I.V.		○		EOS↓ LYM↓	IL-5↓ IL-13↓ PGE2↓ cysLTs↓	↓	ND	107
LXA4 analog	I.V.		○		EOS↓ LYM↓	IL-4↓ IL-5↓ IL-13↓ IL-10↓CCL5 → cysLTs↓	↓	ND	108

Abbreviation: SPM, specific proresolving mediator; I.V., intravenous; I.N., intranasal; EOS, eosinophil; LYM. Lymphocyte; MF, macrophage; NK, natural killer cell; AHR, airway hyperresponsiveness; ND, no data.

Table 2
Impaired biosynthesis of SPM in patients with asthma (severe asthma, asthma exacerbation, AERD, and bronchoconstriction).

SPM	Disease	Clinical sample	Cell type	Findings	Reference
PD1	Severe asthma	WB	EOS	Decreased PD1 synthesis in eosinophils from severe asthmatics	21
	Asthma exacerbation	EBC		Decreased PD1 concentration during asthma exacerbation	94
LXA4	Severe asthma	BALF, EBBs, WB	NEU, EOS, MONO, LYM	Decreased LXA4 concentration in BALF and ALXR expressions on granulocytes in severe asthma	12
		BALF	Alveolar MFAlveolar MΦ	Lower LXA4 generation in alveolar MF from severe asthmatics compared with non-severe asthmatics	13
		EBC		The LXA4/LTB4 ratio is decreased in severe asthma	14
		EBC		Lower LXA4 concentration in severe to moderate asthma than in intermittent asthma and healthy status	15
		WB		Lower LXA4 synthesis in severe asthma than in moderate asthma with higher CysLTs synthesis	16
		WB		Lower LXA4 generation in severe asthma than in mild asthma	17
		WB	LEU	Decreased 15-LOX expressions in leukocytes and LXA4 concentration in severe asthma than in mild to moderate asthma	18
		Sputum		Lower LXA4 concentration in severe asthma than in mild asthma with higher IL-8 concentration	19,20
	AERD	WB		Lower LXA4 and 15-epi LXA4 synthesis in AIA than in ATA	109
		Urine		Lower 15-epi LXA4 concentration in AIA	110
	Asthma exacerbation	EBC		Lower LXA4 concentration in asthma than in status asthmatics	111
	Bronchoconstriction	WB		Lower LXA4 concentration after exercise in mild asthma	112

Abbreviation: AERD, aspirin-exacerbated respiratory disease; BALF, bronchial alveolar lavage fluid; EBBs, endobronchial lung biopsy; WB, whole blood; EBC, exhaled breath conensate; NEU, neutrophil; EOS, eosinophil; MONO, monocyte; LYM, Lymphocyte; MF, macrophage; LEU, leukocytes; CysLTs, cysteinyl leukotrine; LOX, lipoxygenase; ATA, aspirin-tolerant asthma; AIA, aspirin-intolerant asthma.

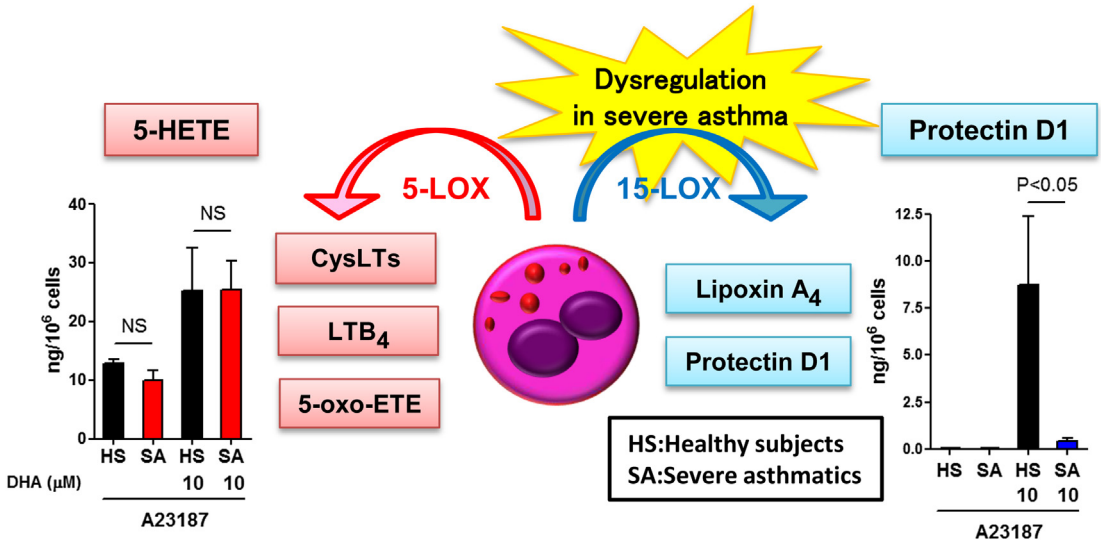

Fig. 2. Dysregulation of 15-lipoxygenase pathway in eosinophil from patients with severe asthma. There was a surprisingly marked decrease in the biosynthesis of PD1 by stimulated peripheral blood eosinophils harvested from patients with severe asthma. In contrast, the levels of 5-HETE, a 5-lipoxygenase-dependent metabolite of arachidonic acid, were similar in patients and healthy subjects, suggesting a selective dysregulation of the 15-lipoxygenase pathway.

Several reports showed decreased biosynthesis or levels of LXA4, a potent anti-inflammatory lipid mediator with suppressive effects on allergic airway inflammation *in vivo*[107,108] in BALF,[12] exhaled breath condensate,[14,15] whole blood,[16–18] and sputum[19,20] of severe asthmatics. Bhavsar et al., demonstrated that the alveolar macrophage was one of the specific cell types with impaired LXA4 biosynthetic capacity.[13] Similar defects in LXA4 synthesis were observed in aspirin-exacerbated respiratory disease (AERD),[109,110] asthma exacerbation,[111] and exercise-induced bronchoconstriction in asthma.[112] Those observations are concordant with our observation of selective dysregulation of PD1 synthesis in human eosinophils, and we propose that impaired fatty acid metabolism may contribute to the pathogenesis of severe asthma. In addition, these observations suggest that dysregulation of a negative feedback system via these pro-resolving molecules might be the underlying pathophysiology in severe asthma. Omega-3 fatty acid supplements might not provide sufficient anti-inflammatory activity because of impaired enzymatic activities in asthma patients. The administration of PD1 or LXA4, or of a molecule that can enhance their synthetic activities, might offer a promising therapeutic strategy for severe asthma.

Conclusion

Epidemiological and observational studies strongly supported the efficacy of omega-3 fatty acids in the prevention or amelioration of asthma and allergic diseases. Molecular mechanisms have been revealed in part by the identification of fatty acid bioactive metabolites. Downstream metabolites generated via lipoxygenase and cyclooxygenase, the specialized pro-resolving mediators

(SPM), possess anti-inflammatory properties, offering a more precise understanding of these benefits in inflammatory responses.

Lipidomic analyses revealed dysregulated fatty acid metabolism in patients with allergic diseases, especially severe asthma. The mechanism of dysregulation in the 15-lipoxygenase pathway and its relationship to asthma phenotype (atopy, gender, age, inflammatory cell type, etc.), medication (corticosteroid, leukotriene receptor antagonist, anti-IgE antibody, etc.), or cytokines/chemokines remain to be determined. Further studies of omega-3 fatty acid metabolism and SPM functions might provide therapeutic targets for the prevention and treatment of asthma and other allergic diseases.

Conflict of interest

The authors have no conflict of interest to disclose.

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