ISSN 2304-3415, Russian Open Medical Journal
2023. Volume 12. Issue 2 (June). Article CID e0201
DOI: 10.15275/rusomj.2023.0201

Review

Polyunsaturated fatty acids and lipid mediators controlling chronic inflammation in asthma

Oxana Yu. Kytikova, Yulia K. Denisenko, Tatyana P. Novgorodtseva, Ivan S. Kovalenko, Marina V. Antonyuk

Vladivostok Branch of Far Eastern Scientific Center for Physiology and Pathology of Respiration – Research Institute of Medical Climatology and Rehabilitation Therapy, Vladivostok, Russia

Received 1 February 2023, Accepted 28 March 2023

Abstract: Asthma is a common chronic heterogeneous inflammatory respiratory disease with complex pathogenesis. Chronic lung inflammation can be the result of a defect in the resolution of the inflammatory process caused by an imbalance between the synthesis of proinflammatory and pro-resolving lipid mediators. The identification of immunomodulatory effects of eicosanoids, specialized pro-resolving mediators (SPMs), and endocannabinoids synthesized from polyunsaturated fatty acids (PUFAs) allows taking a fresh look at the ways of controlling inflammation rather than solely at its mechanisms. The use of ω-3 PUFA-containing food supplements in combination with standard therapy leads to improved asthma control due to the ability of ω-3 PUFAs to stimulate SPM synthesis and inhibit intracellular signaling pathways of inflammation. Lipid mediators are agonists of peroxisome proliferator-activated receptors (PPARs) and glucocorticoid receptors (GR) that have anti-inflammatory properties. The receptors that are widely expressed in the pulmonary epithelium, endothelium, dendritic cells, eosinophils, fibroblasts, and macrophages play an important role in the regulation of immunometabolic homeostasis in the bronchopulmonary system. Our review systematizes the published data on the properties and mechanism of action of biologically active ω-3 and ω-6 PUFAs involved in the inflammatory process in asthma. Also, this article presents the prospects of using ω-3 PUFAs for the resolution of inflammation in asthma.

Keywords: asthma, polyunsaturated fatty acids, endocannabinoids, eicosanoids, pro-resolving lipid mediators, chronic inflammation.

Cite as Kytikova OYu, Denisenko YuK, Novgorodtseva TP, Kovalenko IS, Antonyuk MV. Polyunsaturated fatty acids and lipid mediators controlling chronic inflammation in asthma. *Russian Open Medical Journal* 2023; 12: e0201.

Correspondence to Oxana Yu. Kytikova. Address: 73g Russkaya St., Vladivostok 690105, Russia. Phone: +74232788201. E-mail: kytikova@yandex.ru.

Introduction

Asthma is a common chronic heterogeneous inflammatory respiratory disease that affects about 300 million people worldwide and is characterized by wheezing, coughing, shortness of breath, reduced expiratory airflow, hyperresponsiveness, airway remodeling, and mucus overproduction [1, 2, 3].

Asthma includes phenotypes and endotypes that differ in trigger factors, the degree of control over the disease, the nature of the immune response [4, 5]. The asthma phenotypes reflect clinical and physiological signs and trigger factors, and allow predicting the efficacy of treatment and controlling the dynamics of the disease development [6]. There are several asthma phenotypes: allergic asthma, non-allergic asthma, late-onset asthma, asthma with fixed airflow obstruction, and asthma in obese patients [7]. The asthma endotypes are distinguished based on specific pathobiological markers [8]. The Th2 (T helper 2 cells) asthma endotype is associated with the recruitment of type 2 innate lymphoid cells (ILC2), IgE-secreting B cells, and eosinophils [9]. This endotype may include subendotypes characterized by high levels of interleukins (IL)-5, IL-13 or IgE. The Th2 endotype includes early-onset asthma in children and adolescents, eosinophilic asthma in adults, aspirin-induced asthma, asthma-COPD overlap syndrome (ACOS), etc. The patients without atopy and allergy symptoms have the non-Th2 endotype [10]. The activation of bronchial epithelial cells, along with a production of IL-33, IL-25, IL-17 and thymic stromal lymphopoietin (TSLP), are observed in this type of inflammation. The Th17 endotype is diagnosed in steroid-resistant asthma [11]. The mixed Th2/Th17 endotype is known as well [12]. Non-Th2 asthma endotype includes exercise-induced asthma, asthma associated with obesity, late-onset asthma, asthma in smokers, or neutrophilic asthma in non-smokers, to name a few.

However, even the detection of asthma phenotypes and endotypes aimed at choosing effective therapeutic strategies for relieving the symptoms of the disease does not allow neutralizing chronic inflammation in the bronchopulmonary system [13]. The number of asthma patients worldwide will be approaching 400 million people during next five years [14]. The high prevalence of this pathology is associated with reduced life quality in patients, difficulties in controlling the disease symptoms, patient resistance to glucocorticosteroids (GCS), and economic burden on the health care system [7]. Asthma treatment involves inhaled β2-adrenergic receptor (β2-AR) agonists, inhaled and systemic GCSs, and leukotriene synthesis inhibitors (LTSIs) in combination with leukotriene receptor antagonists (LTRAs) [15]. Most asthma patients respond well to GCS monotherapy or its combination with long-acting β2-agonists and/or LTRAs, which leads to the achievement and maintenance of the disease control. At the same time, such therapy is not effective enough in 5-10% of cases [16]. Besides, extended GCS administration results in numerous side

effects, which reduces the efficacy of treatment [17, 18]. Hence, further studies of the regulatory mechanisms of inflammation and ways of its resolution in asthma are essential.

Impaired inflammation resolution mechanisms play an important role in the development of persistent low-grade bronchopulmonary inflammation [13, 19, 20]. The functioning of immunocompetent cells involved in the resolution process depends on the composition of fatty acids (FAs) in their cell membranes, dietary intake of FAs, and the capability to metabolize polyunsaturated fatty acids (PUFAs) [21]. Therefore, the modification of FA composition can lead to disruption of regulatory mechanisms of the inflammatory process [22, 23]. It is well known that ω-3 and ω-6 PUFAs are precursors for the synthesis of proinflammatory eicosanoids, specialized pro-resolving mediators (SPMs) [24, 25], and endocannabinoids [26]. Endocannabinoids are a group of endogenous lipids that influence the resolution of inflammation, but can also increase the production of proinflammatory mediators [27]. The resolution of acute inflammation consists in switching the synthesis of proinflammatory lipid mediators to the formation of SPMs [28]. The impairment of this process underlies the development of chronic inflammation [29, 30, 31, 32, 33]. Therefore, the study of the role of eicosanoids, SPM and endocannabinoids in the regulation of inflammatory responses in bronchial asthma allows us to expand our understanding of the mechanisms of impaired resolution of inflammation and find new targets for asthma treatment. [30, 31, 34].

It is noteworthy that ω-3 PUFAs and SPMs are agonists of nuclear peroxisome proliferator-activated receptors (PPARs) and glucocorticoid receptor (GR) that exhibit anti-inflammatory effects [35]. The activation of PPARs and GR leads to the initiation of the signaling pathways blocking the expression of inflammatory nuclear transcription factors, such as nuclear factor-kappa B (NF-kB) and activating protein 1 (AP-1) [36]. On the contrary, ω-6 PUFAs and their proinflammatory derivates enhance the expression of NF-kB triggering the synthesis of inflammatory cytokines, nitric oxide, etc. [37]. There is evidence that ω-6 PUFAs and their oxidized forms are responsible for the development of resistance to GCSs in some asthma patients via increasing the NF-kB expression and decreasing GR expression [38]. Endocannabinoids are also agonists for several subtypes of PPARs (α/γ/δ) [39, 40, 41]. Therefore, maintaining a balance between ω-3 and ω-6 PUFAs is an important factor determining the inhibition of inflammation by stimulating the formation of SPMs. The results of contemporary studies established that SPMs are potentially the most effective therapeutic targets in asthma and allergic diseases [42]. These results created fundamentally new opportunities for developing an effective strategy for the treatment of chronic inflammatory diseases of the bronchopulmonary system based on correcting the processes of inflammation resolution.

The effectiveness of ω-3 PUFAs intake to correct the lipid metabolism disorders and immune imbalance in asthma is under investigation [43, 44, 45]. Numerous epidemiological studies of the effect of consuming oily fish or supplements containing ω-3 PUFAs on the development of allergic reactions and asthma during pregnancy, breastfeeding, and during different age periods were carried out [46, 47, 48]. These results confirm the protective properties of ω-3 PUFAs and the relationship between a reduction in fish oil intake and elevated number of people suffering from asthma or other allergic diseases. At the same time, there are many conflicting data on the effectiveness of ω-3 PUFAs in chronic inflammation [49, 50]. Therefore, despite the prospects and great interest in the therapeutic potential of ω-3 PUFAs, the mechanisms of their anti-inflammatory action require clarification.

This review systematizes general knowledge on the biosynthesis and metabolic transformations of long-chain ω-3 and ω-6 PUFAs, their functions as precursors for the formation of proinflammatory and specialized pro-resolving lipid mediators. A contemporary view of the role of lipid mediators in the pathogenesis of chronic inflammation in asthma is highlighted. Some clinical aspects of the anti-inflammatory and pro-resolving action of ω-3 PUFAs are described. Prospects for the use of ω-3 PUFAs aimed at the resolution of chronic bronchopulmonary inflammation are shown.

The role of ω3 and ω6 polyunsaturated fatty acids

FAs are carboxylic acids with a carbon chain containing carboxyl and methyl groups at the ends. FAs are classified into saturated (with no double bonds) and unsaturated. The latter are further classified into monounsaturated (possessing one double bond) and polyunsaturated (containing from two to six double bonds). PUFAs are classified with respect to the position of the first double bond into ω-9, ω-7, ω-6, and ω-3 FAs [51, 52]. According to the length of the carbon chain (C), FAs can be divided into long-chain (C12-C22), medium-chain (C7-C12) and short-chain (C2-C6). Medium- and short-chain FAs are synthesized *de novo* or are a result of fat consumption. Short-chain FAs are synthesized in the intestine and then enter the circulatory system. Since some ω-3 and ω-6 PUFAs are essential (α-linolenic and linoleic acids), their sufficient intake with food is a prerequisite for the normal functioning of the body [53, 54].

The stages of the synthesis of ω-6 PUFAs from linoleic acid and ω-3 PUFAs from α-linolenic acid, as well as enzymes involved in PUFA biosynthesis, are presented in *Table* 1.

Table 1. Biosynthesis of ω-3 and ω-6 PUFAs

ω-6 PUFAs synthesized from linoleic acid (18:2ω6)		*ω-3 PUFAs synthesized from α-linolenic acid (18:3ω3)*	
PUFA name, formula	Enzymes involved in PUFA biosynthesis	PUFA name, formula	Enzymes involved in PUFA biosynthesis
γ-linolenic acid (18:3ω6)	FADS2	stearidonic acid (18:4ω3)	FADS2
dihomo-γ-linolenic acid (20:3ω6)	ELOVL5	eicosatetraenoic acid (20:4ω3)	ELOVL5
arachidonic acid (20:4ω6)	FADS1	eicosapentaenoic acid (20:5ω3)	FADS1
adrenic acid (22:4ω6)	ELOVL5	ω3 docosapentaenoic acid (22:5ω3)	ELOVL2
tetracosatetraenoic acid (24:4ω6)	ELOVL2	tetracosapentaenoic acid (24:5ω3)	ELOVL2
tetracosapentaenoic acid (24:5ω6)	FADS2	tetracosahexaenoic acid (24:6ω3)	FADS2
ω6 docosapentaenoic acid (22:5ω6)	β-oxidation in peroxisomes	docosahexaenoic acid (22:6ω3)	β-oxidation in peroxisomes

Table 2. Eicosanoids and their functions

Eicosanoids	*Enzymes*	*Receptors*	*Synthesis site*	*Functions*	*References*
Leukotrienes (LTs)					
LTB_4	5-LOX	LTB4R1	leukocytes, platelets	bronchoconstriction, chemoattractant for neutrophils, plasma exudation, reduction of lung parenchyma, activation of lipid metabolism,induction of release of lysosomal enzymes from neutrophils,participation in immune responses, inhibition of apoptosis	[61, 68, 69]
		LTB4R2 (BLT1, BLT2)	lungs		
CysLT: LTC_4 LTD_4 LTE_4 LTF_4	5-LOX	CysLT1R	mast cells,leukocytes, airway smooth muscle cells, macrophages, eosinophils	proinflammatory mediator, bronchoconstrictor, induction of hyperresponsiveness and edema of the bronchi, slow-acting mediator of anaphylaxis, overexpression in several types of cancer, increase in the tone of smooth muscles of the gastrointestinal tract, participation in airway remodeling	[61, 62, 70-72]
		CysLT2R	lung macrophages, airway smooth muscle cells, peripheral blood leukocytes		
		CysLT3R	airway brush cells		
Prostanoids (PGs and TXs)					
PGI_2 (prostacyclin)	COX 1/2	IP	dendritic cells, type 2 innate lymphoid cells (ILC2), blood vessel walls	vasodilation, myocardial protection, inhibition of platelet aggregation, inhibition of smooth muscle proliferation	[73, 74]
PGE_2	COX 1/2	prostaglandin E2 receptor 1 (EP1)	mast cells, pulmonary veins, keratinocytes, myometrium, colon smooth muscles	bronchoconstriction,smooth muscle contraction in gastrointestinal tract,mediation of hyperalgesia,suppression of pain, triggering colon cancer development in mice, triggering hypertension in diabetic mice, increased differentiation of uncommitted T-cell lymphocytes to the Th1 cell phenotype, differential involvement in the etiology of acute brain injury	[75-78]
		prostaglandin E2 receptor 2 (EP2)	many cell types	bronchodilation, relaxation of smooth muscle in gastrointestinal tract, vasodilation	
		prostaglandin E2 receptor 3 (EP3)	many cell types	activation of autonomic neurotransmitters, contraction of smooth muscle in gastrointestinal tract, stimulation of intestinal mucous secretion, inhibition of gastric acid secretion, uterus contraction, lipolysis inhibition, activation of platelet response to their agonists, activation of atherothrombosis	
		prostaglandin E2 receptor 4 (EP4)	heart, small intestine, lungs, kidney, thymus, uterus, dorsal root ganglia, brain	tumor growth, angiogenesis, lymphangiogenesis	
$PGF_2\alpha$	COX 1/2	FP	uterus, eye	bronchoconstriction, uterus contraction, urinary bladder contraction,vasoconstriction in cerebral circulation	[79-81]
PGD_2	COX 1/2	DP1 (D prostanoid)	platelets, endothelial cells, eosinophils, basophils, mast cells, T cells, different subsets of macrophages	bronchoconstriction, mucus hypersecretion, leukocyte chemotaxis, inhibitor of platelet aggregation; activation of eosinophils, mast cells and Th2 cells; constriction of vascular and airway smooth muscle	[82-86]
		DP2 (chemoattractant receptor-homologous molecule on Th2 cells (CRTH2) or CD294)	eosinophils, basophils, mast cells, Th2 cells, Th2A cells, ILC2, alveolar macrophages		
TXA_2	COX 1/2	TPα, TPβ	platelets, macrophages, neutrophils,endothelial cells	activation of platelets and platelet aggregation; vasoconstriction	[87-94]
TXB_2	COX 1/2				[85]
HETEs					
7-HETE 10-HETE 12-HETE 13-HETE 15-HETE 16-HETE 17-HETE 18-HETE 19-HETE 20-HETE	CYP			20-HETE increases hypertension, systemic vasoconstriction and tumor growth; 20-HETE controls vascular smooth muscle and endothelial cells by influencing their proliferation, migration, survival, and tubule formation; control of cerebral blood flow and integrity of the blood-brain barrier; 12S-HETE is a vasoconstrictor	[63-66, 93]

The biosynthesis and metabolic transformations of ω-6 and ω-3 PUFAs are mediated by the same enzymes responsible for elongation and desaturation: elongase 2 (ELOVL2), elongase 5 (ELOVL5), Δ5 desaturase (delta-5 desaturase, or D5D, also known as FADS1), and Δ6 desaturase (delta-6 desaturase, or D6D, also known as FADS2) [55]. Elongases are responsible for the lengthening of the PUFA hydrocarbon chain. Desaturases catalyze the transformation of a single bond between carbon atoms into the double unsaturated bond (C=C) [56]. Since the enzymes involved in the synthesis of 20-22 PUFAs are universal for both ω-3 PUFA and ω-6 PUFAs, these FAs compete for the enzyme system. The mechanism underlying the development of a certain metabolic pathway mediated by elongases and desaturases is still not fully understood.

Subsequently, the metabolic transformations of PUFAs follow the enzymatic oxidation pathways for eicosanoid (proinflammatory mediators) and SPM production (pro-resolving mediators) [30]. PUFAs are released from membrane phospholipids with the participation of phospholipase A2 (PLA2). The latter can be of three different types: cytosolic calcium-dependent PLA2 (cPLA2), cytosolic calcium-independent PLA2 (iPLA2), and secreted PLA2 (sPLA2)) [57]. The synthesis of eicosanoids and SPMs are catalyzed by cyclooxygenases (COX1 and COX2), lipoxygenases (5-LOX, 8-LOX, 12-LOX, 15-LOX), cytochrome P450 (CYP 450) and leukotriene A4 hydrolase (LTA4H) [58, 59].

The role of eicosanoids in asthma pathogenesis

Eicosanoids include leukotrienes (LTs), prostanoids (prostaglandins – PGs, cyclopentenone PGs, thromboxanes – TXs), and metabolites of hydroxyeicosatetraenoic acids (HETEs), epoxyeicosatrienoic acids (EETs), dihydroxyeicosatrienoic acids (DHETs) [60-68].

LTs are classified into LTB4, LTB5 (the less potent LTB4 analog), as well as LTC4, LTD4, LTE4, LTF4 that belong to the group of cysteinyl leukotrienes (CysLT) and are formed after the conversion of arachidonic acid (AA) to LT A4 [61, 62, 69-72].

Prostanoids include PGs (prostaglandin I2 [PGI2 or prostacyclin], PGD2, PGE2, PGF2α), cyclopentenone PGs (15-deoxy-Δ-12,14-prostaglandin J2 [15d-PGJ2], Δ12-PGJ2, PGJ2, PGC2, PGA1, PGA2), and TXs (thromboxane A2 [TxA2], TXB2) [73-90].

Eicosanoids are involved in the regulation of various processes occurring in the cell [58, 67-94] (*Table 2*).

Leukotrienes

LTB4 plays an important role in airway inflammation [61]. LTB4 mediates plasma exudation, thereby causing the mucosal edema. This LT is a neutrophil chemoattractant: it stimulates macrophages to produce interferon-alpha (IFN-alpha), IL-17, IL-6, and IL-1-beta. LTB4 and LTB5 bind to the LTB4R1 and LTB4R2 receptors (also known as BLT1 and BLT2, respectively).

CysLTs are mainly secreted by mast cells and leukocytes [70] and act via three major G protein-coupled receptors (CysLT1R, CysLT2R, and CysLT3R) [61]. The biosynthesis of LTC4 in mast cells is catalyzed by cPLA2 α, 5-LOX, 5-lipoxygenase-activating protein (FLAP) and LTC4 synthase (LTC4S). The enzyme cPLA2α induces AA synthesis; 5-LOX and FLAP oxidize AA to produce LTA4, and LTC4S conjugates LTA4 with glutathione to synthesize LTC4. Cellular proteases metabolize LTC4 to generate more stable products (LTD4 and LTE4) [71]. Then, all three LTs bind to CysLTR1 and CysLTR2 receptors. It is well known that CysLTs are proinflammatory mediators, powerful bronchoconstrictors; they cause hyperresponsiveness and edema of the bronchi, and are involved in airway remodeling. The role of CysLTs in the development of allergies and asthma was extensively studied in this regard [61, 70]. LTD4 binds to CysLT1R and is the most potent bronchoconstrictor [71]. Many studies established that CysLT1R antagonists, such as montelukast, have a beneficial effect on asthmatics, especially GCS-resistant asthma patients [61]. LTD4 can induce the inflammatory reaction mediated by airway epithelial cells and promote airway remodeling in both allergic and non-allergic asthma [72].

Table 3. Pro-resolving lipid mediators and their functions

Mediators		*Receptors*	*Synthesis site*	*Functions*	*References*
MMaR	MaR1	Leucine-rich, repeat- containin g, G protein–coupled, receptor 6 (LGR6)		resolving, regenerative and antiplatelet effects	[20, 31, 34, 95-101]
	MaR2	–		modulation of adaptive immune responses in peripheral blood lymphocytes	
LLX	LXA4	antagonist for ALX/FPR2; antagonist for DRV/GPR32	leukocytes, epithelial cells	chemotaxis and migration of macrophages and neutrophils to the inflammation area, blocking lipid peroxidation, activation of NF-kB and inhibition of the synthesis of proinflammatory cytokines, vasodilatation, blocking inflammation, activating resolution and recovery processes, attenuation of neuroinflammation via modulating T cell responses	[102-104]
RRv	RvE1	antagonist for BLT1, agonist for ERV/Chemokine like receptor 1 (CMKLR1)/ChemR23		reduction in airway hyperresponsiveness, regulation of neutrophil chemotaxis, activation of phagocytosis and synthesis of anti-inflammatory cytokines, tissue regeneration, control of neutrophil chemotaxis	[31, 105-116]
	RvE2			reduction in airway hyperresponsiveness, control of neutrophil chemotaxis, activation of phagocytosis and synthesis of anti-inflammatory cytokines, tissue regeneration, regulation of neutrophil chemotaxis, activation of phagocytosis and synthesis of anti-inflammatory cytokines	
	RvE4			stimulating macrophage efferocytosis	
	RvD1	ALX/ FPR2 G protein-coupled receptor 32 (GPR32)		suppression of eosinophilia, suppression of synthesis of proinflammatory mediators, inhibition of macrophage apoptosis, modulation of adaptive immune responses in human peripheral blood lymphocytes	
	RvD2	GPR18/RvD2 receptor		modulation of adaptive immune responses in peripheral blood lymphocytes	
PD	PD1	GPR37		reduction in airway hyperresponsiveness, anti-inflammatory and europrotective effects	[98, 117, 118]

Table 4. Peroxisome proliferator-activated receptors and their natural ligands

PPAR isoforms	*Synthesis site*	*Natural ligands*
PPARα (NR1C1)	Liver, kidneys, skeletal muscles, heart, brown adipose tissue, epithelial cells, lymphocytes, dendritic cells of the mucous membrane in the respiratory tract, pulmonary epithelium, endothelium, eosinophils, fibroblasts, macrophages	PUFAs, anandamide, 2-AG, OEA, SPMs, LTB4, 8(S)-HETE, AA, EPA, LDL, DHA, 17-oxoDHA
PPARβ/δ (NR1C2, PPARδ, PPARβ, hNUC1, FAAR)	Brain, liver, skin, adipose tissue, skeletal muscles, dendritic cells of the mucous membrane in the respiratory tract, pulmonary epithelium, endothelium, eosinophils, fibroblasts, macrophages	PUFAs, AA, EPA, DHA, 8(S)-HETE, anandamide
PPARγ (NR1C3)	Adipose tissue, colon, spleen, dendritic cells of the mucous membrane in the respiratory tract, pulmonary epithelium, endothelium, eosinophils, fibroblasts, macrophages	PUFAs, AA, EPA, DHA, 17-oxoDHA, RvE1, PD1, LXA4, 8(S)-HETE, 15(S)-HETE, PGA1, PGA2, PGD2, 15d-PGJ2, anandamide, 2-AG, 15D-PGJ2-glycerol ether

Prostanoids

Prostanoids are a large group of inflammatory mediators (PGs and TXs) derived from AA [73]. Prostaglandins are powerful vasodilators, inhibit platelet aggregation, and regulate smooth muscle cell contraction. Most PGs have a proinflammatory action (for example, PGE2 and PGD2), but cyclopentenone PG (PGA2 and 15d-PGJ2) is characterized by anti-inflammatory and antioxidant effects. Structural differences between PGs and the variety of their receptors (G protein-coupled receptors) determine different biological activities of PGs and their opposite effects in different tissues.

The interaction between PGI2 and the prostacyclin receptor (the prostaglandin I2 receptor or IP) leads to activating vasodilation and myocardial protection suppressing platelet aggregation and inhibiting smooth muscle proliferation [73, 74].

PGE2 is among the most abundant proinflammatory PGs. It causes vasodilation and elevated permeability of lung microvessels, which results in accumulating inflammatory cells at the site of infection. PGE2 increases mucociliary transport and liquid volume of the airway surface, and provokes type 2 T helper cell (Th2) responses. However, PGE2 can also perform pro-resolving functions. The multifunctionality of this PG is associated with the presence of a different type of its receptors [75]. The prostaglandin E2 (PGE2) receptors include the following isoforms: prostaglandin E2 receptor 1 (EP1), prostaglandin E2 receptor 2 (EP2), prostaglandin E2 receptor 3 (EP3), prostaglandin E2 receptor 4 (EP4) [76]. EP1 receptor mediates hyperalgesia, suppresses pain, stimulates colon cancer development in mice, induces hypertension in diabetic mice, and enhances the differentiation of uncommitted T cell lymphocytes to the Th1 cell phenotype differentially involved in etiology of acute brain injuries. The activation of EP2 promotes the development of inflammation by regulating B cell immunoglobulin class, and maturation of T lymphocyte CD4−CD8− cells to CD4+CD8+ cells. However, EP2 activation also suppresses inflammation by affecting immune cells (neutrophils, monocytes, macrophages, dendritic cells, NK cells, fibroblasts) [77]. EP3, like EP4, have different functions; at the same time many of them were found only in animals, but not in humans. EP3 play an important role in reducing allergic reactivity (at least in mice). H. Gao et al. demonstrated that cough induced by PGE2 and depolarization of the vagus nerve in vitro were inhibited by the administration of EP3 receptor [78].

PGF2α is a potent bronchoconstrictor and inflammatory mediator [79]. This prostaglandin is involved in the regulation of lipopolysaccharide-induced systemic inflammation [80]. Additionally, PGF2α concentration in blood plasma is a marker of oxidative stress in asthma [81].

PGD2 is expressed on eosinophils, basophils, Th2 cells, ILC2, macrophages, as well as mast, epithelial and smooth muscle cells [74, 82]. Prostanoid PGD2 causes bronchospasm, vasodilation and regulates functioning of immune cells through binding receptors DP1 (receptor 1 PGD2) and DP2 (receptor 2 PGD2). DP1 is expressed on platelets, eosinophils, basophils, T cells, macrophages, and endothelial cells [83]. It mediates vasodilatation, induces smooth muscle relaxation and eosinophil apoptosis. DP2 receptor has a wide range of ligands: PGD2 and its metabolites, including Δ12PGD2, Δ12PGJ2, 15-deoxy-Δ12,14PGD2, 15-deoxy12,14PGJ2, and 9α11βPGF2 [84]. PGD2, just as PGF2α, is a bronchoconstrictor and mediator of airway inflammation [79]. It was shown that PGF2α and PGD2 levels positively correlated with the severity of airflow obstruction in asthma, while PGE2 was not associated with lung functioning [85]. Concentrations of PGD2 and CysLT in exhaled air condensate and sputum were remarkably higher in asthma patients than in healthy subjects, and these parameters varied depending on the severity of asthma [86].

The analysis of metabolites of PGs, CysLTs, and isoprostanes provides the basis for a new, noninvasive approach to molecular phenotyping of asthma in adults and adolescents [62]. Concentrations of these metabolites in healthy subjects (except for PGE2) are not associated with age, body mass index, or sex. High levels of LTE4 and PGD2 are related to lower lung function, increased concentration of nitric oxide and increased amounts of eosinophils in the blood, sputum, and urine in adolescents with asthma [62].

TxA2 is produced by platelets, neutrophils, monocytes, macrophages, and cells of the lung parenchyma [87, 88]. It is known that PG can be converted to TxA2 by the TxA2 synthase; the latter is expressed in the lungs, kidneys, liver, monocytes and megakaryocytes. TxA2 transmits signal through the TP receptor (thromboxane receptor) (TPα and TPβ). TPα activates adenylate cyclase that leads to an increase in cAMP levels and the induction of intracellular signaling, while TPβ inhibits it. TxA2 is activated during tissue damage and inflammation, causing platelet aggregation and vasoconstriction. At the same time, PGI2 inhibits platelet aggregation and smooth muscle proliferation and induces vasodilation. S. Braune et al. described the effect of prostanoids on platelets, which are key participants in thrombosis and hemostasis. [89]. Since TxA2 and PGI2 have antagonistic effects on thrombosis and atherogenesis, their balance is necessary for maintaining vascular homeostasis. The activation of TP affects platelet aggregation and airway smooth muscle contraction; therefore, increased TxA2 activity may play a role in the pathogenesis of asthma. Interestingly, mast cells release PGD2 under in vitro conditions, but inhibition of this process by using hematopoietic prostaglandin-D-synthase (hPGDS) results in PGE2 and TXA2 secretion [90]. Contrarywise, if thromboxane synthase activity is

suppressed, PGD2 level increases. The authors emphasized that it is necessary to prove the presence of these changes in vivo and their clinical significance.

TXA_2 is an extremely unstable metabolite that is hydrolyzed to stable but physiologically inert TxB_2 in the absence of the enzyme [91]. TxB_2 correlates with the severity of airflow obstruction in asthma [85, 92-94].

Thus, prostanoids are involved in many physiological and pathophysiological processes. Further study of the role of eicosanoids in asthma pathogenesis is necessary for developing personalized treatment of this pathology.

Pro-resolving lipid mediators in asthma pathogenesis

SPMs include resolvins (Rvs), lipoxins (LXs), protectins (PDs), maresins (MaRs), and 15-epi-lipoxin A4 [34, 95-101]. SPMs act on receptors of various cells of the immune system: lymphocytes, neutrophils, macrophages, endothelial and epithelial cells [20]. They limit the production of proinflammatory mediators, including PGs, LTs, and selective cytokines; stimulate bacterial phagocytosis and efferocytosis of apoptotic cells, thereby ensuring the restoration of homeostasis (*Table* 3).

Decreased SPM synthesis is observed in asthma, which contributes to the chronicity of the inflammatory process in the bronchopulmonary system [20, 34, 96]. Therefore, the administration of SPMs can be an effective way to treat asthma. However, insufficient understanding of the SPM signaling pathways and rapid inactivation of SMPs limit their translational potential. Stable low-molecular-weight SPM mimetics and agonists of their receptor became new potential medicinal drugs. Recently, preclinical studies demonstrated that they can effectively reduce asthma manifestations by the resolution of inflammation [42].

Maresins

MaR biosynthesis is initiated in macrophages. The 12-LOX enzyme converts docosahexaenoic acid to 13S, 14S-epoxymaresin; then hydrolase (or epoxide hydrolase) stimulates the formation of MaR1 and MaR2 from this metabolite. Recently discovered SPM sulfido-conjugates (SPM-SCs) are also synthesized from 13S, 14S-epoxymaresin [31, 34, 98]. The SPM group includes maresin conjugates in tissue regeneration (MCTRs), protectin conjugates in tissue regeneration (PCTRs), and resolvin conjugates in tissue regeneration (RCTRs) [99]. MCTR1 is formed from 13S, 14S-epoxymeresin (under the influence of glutathione-s-transferase mu4 [GSTM4] and/or leukotriene-C4-synthase [LTC4S]). Then gamma-glutamyltransferase (GGT) converts MCTR1 to MCTR2, which is followed by conversion into MCTR3 via dipeptidase (DPEP). MaRs are believed to act as potent mediators of the inflammatory activity of macrophages, thereby contributing to the resolution of acute inflammation and tissue regeneration. MaR1 exhibits powerful resorption, regenerative, and antiplatelet properties [100]. MaR2 modulates an adaptive immune response in human peripheral blood lymphocytes. These data provide new possibilities for developing approaches to the modulation of chronic inflammation via affecting MaR2 [101]. MCTRs are the most common CysLTs in the lungs of healthy people, while other CysLTs are widely expressed in patients with asthma [31, 98]. MCTRs act as regenerating agents with anti-inflammatory properties [34]. The decreased MCTR1 level and the increased MCTR3 level in asthma indicate the enzymatic conversion of MCTR1 to MCTR3. However, this process is slower than the conversion of LTC4 to LTD4 and LTE4. In patients with severe asthma, CysLT production is elevated, while LX synthesis is reduced. Particularly, MCTRs was shown to block the LTD4-induced contraction of the respiratory muscles and facilitate the resolution of airway allergic response in mice [99].

Lipoxins

LXs (LXA4 and LXB4) are derivatives of AA, but unlike eicosanoids, they exhibit pronounced anti-inflammatory properties and activate the processes of resolution and recovery [102]. LXs can be formed in several ways. For example, LXA4 and LXB4 are synthesized by neutrophils through 5-LOX pathway; and by eosinophils, neutrophils and macrophages via 5-LOX and 15-LOX; while LXA4 is generated by platelets via 12-LOX. LXs suppress IL-8 secretion by leukocytes and epithelial cells and also stimulate macrophage efferocytosis [103]. LXA4 and LXB4 are derivatives of LOX-mediated metabolism and important pro-resolving mediators in asthma [104]. The therapeutic potential of 15-epi-LXA4 for the resolution of acute lung inflammation has been demonstrated [97]. It was noted that LXs, PGE2 and 15d-PGJ2, are capable of inducing reprogramming of macrophages to the M2 phenotype in vitro and in vivo. Although PGE2 and LXA4 exhibited beneficial effects in patients with asthma, further investigation of their mechanisms of action is required, since, according to the obtained results, PGE2 caused side effects and LXA4 had low stability [104]. Taking into account the discovered disorders in LX production in asthma, these mediators may be of significant interest as a therapeutic target.

Resolvins

Resolvins are biosynthesized from ω-3 PUFAs: eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) [105]. Rv E-series (RvE1, RvE2) are derived from EPA, and Rv D-series (RvD1, RvD2, RvD3, RvD4, RvD5, RvD6) are formed from DHA [106, 107].

The anti-inflammatory effect of RvE1 is associated with its interaction with PPARs and blocking of NF-kB expression [108]. The RvE1 receptors are LT B4 receptor 1 (BLT1) and G-protein coupled receptor (Chemerin Receptor 23 – ChemR23). RvE1 has an antagonistic effect on BLT1 and blocks biological effects of proinflammatory LTs. At the same time, RvE1 exhibits a synergistic effect on ChemR23, inhibits the activation of NF-kB and enhances phagocytosis [109]. RvE2 exerts a biological effect similar to RvE1, regulates neutrophil chemotaxis, and activates phagocytosis and synthesis of anti-inflammatory cytokines. RvD1 acts through LX A4 receptor (ALX) and G-protein-coupled receptor 32 (GPR32). Resolvin E4 (RvE4: 5S, 15S-dihydroxy-eicosapentaenoic acid) is a recently discovered resolvin that increases the efferocytosis of apoptotic cells by macrophages [110, 111].

RvD1 and RvD2 arrest the inflammatory process by modulating the adaptive immune response of human peripheral blood lymphocytes [107]. These lipid mediators reduce cytokine production by activating CD8+, Th1 and Th17 cells. Furthermore, they prevent the differentiation of CD4+ T cells into Th1 and Th17 by suppressing their transcription factors. In particular, RvD1 attenuates local and systemic inflammatory responses in sepsis-induced cardiac injury [112].

The mechanism of action of RvD and RvE in bronchopulmonary pathology is under investigation [31, 113, 114, 115]. RvE1 contributes to the resolution of airway inflammation by inhibiting eosinophil and lymphocyte recruitment and the production of IL-6, IL-13 and IL-23. RvE1 reduces airway sensitivity and inflammation in asthmatic mice [114]. Additionally, 17-epi-RvD1 is effective for the resolution of acute lung inflammation [97]. MaR1 and RvD1 inhibit the synthesis of cytokines by ILC2s and thereby participate in the control of ILC2-mediated eosinophilic airway inflammation and diseases [116]. Therefore, these lipid mediators may be the basis for developing a therapeutic strategy to alleviate airway inflammation.

Protectins

Protectins are formed from DHA and are synthesized by a number of cells, including brain cells, monocytes, and $CD4^+$ lymphocytes [117]. PD1 (the main member of the protectin family) exhibits potent anti-inflammatory and neuroprotective actions through interacting with PPARs, blocking NF-κB expression, decreasing COX-2 expression and PG production. PD1 is a regulator of the protein synthesis of the B-cell lymphoma 2 (BCL2) family that has a pronounced antiapoptotic effect.

A decrease in PD1 level was revealed in severe and uncontrolled asthma. Recently, PD1 was identified in exhaled breath condensate in asthma patients during exacerbation of the disease. In addition, PD1 reduces the level of PGD2 involved in airway hyperresponsiveness. The ability of PD1 to inhibit 15-LOX expression and, therefore, to suppress LT biosynthesis was shown as well [98]. It was demonstrated that intravenous injection of PD1 into allergen-sensitized mice prior to aerosol allergen administration prevented the development of airway hyperresponsiveness, as well as eosinophilic and T-cell-mediated inflammation in these animals [98]. Protectin is able to reduce the inflammatory response in lung tissue after sepsis by activating PPARγ and inhibiting phosphorylation and activation of NF-κB p65 [117]. Protectin can modulate the epithelial cell repair, and activate the proliferation of primary rat lung fibroblasts and the differentiation of myofibroblasts [118]. Overall, the anti-inflammatory activity of PD1 indicates its therapeutic potential in asthma.

Endocannabinoids in asthma pathogenesis

The endocannabinoid system performs important functions: from regulating energy balance, metabolism of carbohydrates and lipids to participating in the immune response [119]. Although the greatest number of studies on the biology of endocannabinoid system was carried out in the field of neurology and psychiatry, accumulated data have demonstrated the importance of this system in various diseases such as cancer, Alzheimer's disease, multiple sclerosis, cardiovascular disease, chronic pain, obesity, and asthma [120-122].

This system includes the endocannabinoids, anandamide and 2-arachidonoylglycerol (2-AG), cannabinoid receptors and enzymatic systems involved in their synthesis, transport, metabolism, and decomposition [27]. Anandamide is biosynthesized from N-arachidonoyl phosphatidylethanolamine (NAPE) in humans. In turn, NAPE arises by the transfer of AA from lecithin to the free amine of cephalin via the enzyme N-acyltransferase [123]. Anandamide is synthesized from NAPE by several pathways that involve enzymes such as phospholipase A2, phospholipase C, and *N*-acetylphosphatidylethanolamine-hydrolyzing phospholipase D (NAPE-PLD); 2-arachidonoylglycerol is derived from diacylglycerol (DAG) containing AA. The subsequent metabolism of endocannabinoids by the CYP (cytochrome P450)-mediated mechanism leads to the formation of many highly active eicosanoids with different physiological effects [28].

Cannabinoids bind mainly to CB1 and CB2 receptors [124]. CB1 receptors are expressed in areas of the brain responsible for motor and cognitive functions, memory, learning, positive emotions, regulation of homeostasis and reproduction, body temperature, sleep and wakefulness, as well as in white and brown adipose tissues, liver, skeletal muscles, pancreas, and bronchi [125]. CB2 receptors are localized in lymphoid organs, on B cells, monocytes/macrophages, and eosinophils [126]. The activation of this receptor type on mast cells has a direct anti-inflammatory effect. Current research data indicate the important role of mast cells in the pathophysiology of asthma and reveal the mechanism of their effect on respiratory function.

There are other types of cannabinoid-activated receptors – G-protein coupled receptors. They are located in the central nervous system, intestines, liver, bones, skeletal muscles, and adipose tissue (for example, GPR18, GPR55, GPR119, etc.) [124]. In addition to CB receptors, endocannabinoids can bind and activate ion channels with a transient receptor potential (TRP) [40, 127]. Moreover, 2-AG is an agonist for several subtypes of PPARs [39, 40]. A. Lago-Fernandez et al. analyzed the relationships between endocannabinoids and PPARs in different pathologies, and also the analgesic, antitumor, and neuroprotective properties of various phytogenic, endogenous, and synthetic cannabinoids [128].

Particular attention should be paid to the participation of the endocannabinoid system in the immune response. The mechanism of immunosuppression, mediated by cannabinoids, were studied in vitro and in vivo models of many diseases, such as multiple sclerosis, diabetes, septic shock, rheumatoid arthritis, and allergic asthma [129-132]. The recent review authored by N.E. Kaminski et al. summarized key research on the mechanisms of action of cannabinoids in animals and humans (including meta-analyses and randomized clinical trials), along with the results of genetic analysis of single nucleotide polymorphisms in the CNR1 and CNR2 genes located on CB1 and CB2 receptors, which indicates the important role of these receptors in immune-mediated diseases [129]. Z.P. Espinosa-Riquer et al. demonstrated that 2-AG and its CB2 receptors play an important role in the inhibition of innate immune reactions in vivo [130].

The contribution of the endocannabinoid system in asthma pathogenesis was extensively studied in recent years. It was shown that receptors interacting directly with endocannabinoids, specifically, PPAR-α, GRP 55, TRPV1, CB1, and CB2 [39], were localized in the bronchi of mice [41]. It is known that TRPV, TRPA1, TRPM8, PPARs are involved in asthma pathogenesis [39, 40, 127]. A number of innate immune cells, including airway epithelial cells, dendritic cells, macrophages, natural killer (NK) cells, and group 2 (ILC2) are important in the development of asthma. M.E. Ferrini et al. demonstrated the contribution of allergen-induced CB2 activation in the regulation of the activity of NK cells in chronic lung inflammation [133]. Mice lacking CB2 receptors had an increased number of NK cells in the lungs, along with a reduced amount of ILC2. M. Ferrini et al. proposed that NK cells limit ILC2 response in allergic airway inflammation [133]. It is worth noting that NK cells are regulated by a number of endogenously produced

eicosanoids, including prostaglandins (PGD2, PGE2), and CB2 [133]. Some authors investigated in vitro the effect of 2-AG on the production of cytokines by lung NK cells. It was revealed that this cannabinoid inhibits the synthesis of IFN-γ by studied cells, which indicates that endocannabinoids play a key role in the suppression of cytokine production by NK cells in the lungs via interacting with CB2 receptors. Increased activity of endocannabinoids is observed under conditions of prostaglandin deficiency. Further studies of the effect of CB2 activation on markers of airway inflammation are needed [134]. Future research of the therapeutic potential of endocannabinoids as PPAR agonists in asthma is of great interest.

Cannabinoids or cannabinoid-based medicinal drugs are promising as anti-inflammatory or immunosuppressive agents [129]. However, currently, there is some controversy regarding the advisability of therapeutic use of these compounds [132]. The conflicting effects of endocannabinoids observed in clinical trials are related to high heterogeneity of their receptors and complexity of signaling.

The relationship between eicosanoids, pro-resolving lipid mediators, endocannabinoids and nuclear transcription factors in asthma

Peroxisome proliferator-activated receptors

PPARs are involved in the regulation of inflammatory responses and lipid metabolism [36]. These receptors belong to the superfamily of hormonal nuclear transcription factors with anti-inflammatory properties (48 members) [135]. Three isoforms of PPARs are known: PPARα (NR1C1), PPARβ/δ (NR1C2), and PPARγ (NR1C3). Natural ligands for all PPAR isoforms are PUFAs, endocannabinoids, eicosanoids and their products: 12(S)-HETE, 15(S)-HETE, 13-hydroxyoctadeca-dienoic acid (13-HODE). Other natural ligands for PPARs are SPMs (Rv, PD, MaR, LX, 15-epi-LXA_4) (*Table 4*).

PPARα is produced in the liver, kidney, heart, skeletal muscle, brown adipose tissue, as well as by epithelial cells, macrophages, lymphocytes, and dendritic cells of the respiratory tract mucosa [136]. This receptor isoform stimulates the expression of genes of enzymes involved in β-oxidation and regulates the metabolism of lipids, carbohydrates and amino acids. PPARα reduces the synthesis of proinflammatory mediators and modulates the production of adhesive and chemotactic molecules [36].

PPARβ/δ is expressed in all organs and tissues; however, their synthesis is most pronounced in the brain, liver, skin, adipose tissue, and skeletal muscles [137]. PPARβ/δ is involved in fatty acid oxidation; it regulates plasma lipid and blood glucose levels, increases the sensitivity of cells to insulin, and participates in wound healing [135].

There are three types of PPARγ: PPARγ1 is expressed in all tissues and cells, PPARγ2 is mainly produced in adipose tissue, and PPARγ3 is synthesized in colon, spleen, white adipose tissue and by macrophages. This receptor is an important regulator of cellular homeostasis and energy metabolism [138].

AA metabolites (PGA2 and 15d-PGJ2) modulate PPARγ activity, while 5(S)-HETE, 8(S)-HETE, 8S-HPETE, 15-HETE, and LTB4 interact with PPARα [139]. PPARβ/δ can be activated by prostacyclin and 15-HETE [140]. Nevertheless, 5(S)-HETE, 8(S)-HETE, 15-HETE, and LTB4 are weaker activators [141]. It is well known that the production of PGE2 and PGD2, which are transformed into anti-inflammatory PGA2 and 15d-PGJ2, is increased in inflammation [141].

All PPAR isoforms are expressed in the lung epithelium and endothelium, by dendritic cells, eosinophils, fibroblasts, and macrophages. PPARs modulate lipid homeostasis and are involved in the control of genes responsible for the oxidative metabolism of lipids: carnitine palmitoyltransferase I (CPT1), pyruvate dehydrogenase lipoamide kinase isozyme 4 mitochondrial (PDK4), CYP4A, and acyl-CoA oxidase 1 (ACOX 141) [142, 143]. Wide expression of PPARs in the bronchopulmonary system, their anti-inflammatory effect and their ability to regulate lipid metabolism attracted close attention of scientists as potential therapeutic targets in asthma [35].

Glucocorticoid receptor

GR is ubiquitously expressed and acts as a ligand-dependent transcription factor [144]. In the absence of the ligand, GR is located in the cytoplasm and is part of the complex that includes heat shock proteins (hsp90, hsp70, and hsp56), immunophilins, and p23. Ligand binding to GR results in the translocation of the receptor into the nucleus, where it interacts with DNA [145]. It is assumed that direct binding of GR to DNA activates transcription, while binding of GR to proinflammatory transcription factors suppresses the process [146]. An important coregulator is the peroxisome proliferator-activated γ-coactivator 1-α (PGC1α) that interacts with GR to modulate gene expression. PGC1α forms a stable complex with the ancestral variant of the GR (AncGR2) LBD [147].

The GR receptor has several isoforms, the most studied of which are GRα and GRβ [144]. The GRα isoform stimulates transcriptional activity of GR, while GRβ is involved in disrupting GRα-mediated GR activity. GRβ also regulates many genes associated with the inflammatory process in a GRα-independent manner [148]. The GR receptor modulates the transcription of proinflammatory and anti-inflammatory genes through multiple isoforms initiating various mechanisms.

Glucocorticoids (GCs) used in asthma therapy act via the GR receptor [149]. Inhaled GCs are effective for most asthma patients; however, some patients exhibit poor asthma control even after taking high doses of local or systemic GCs. Targeting GR-associated pathways can overcome GC resistance. GCs have activating and inhibitory effects on the immune system; therefore, they are able to regulate the immune balance between the response to antigens and excessive inflammation [150].

NF-κB

The proinflammatory role of NF-κB is well understood [151]. The NF-κB signalling is involved in the progression of cancer, in particular, in lung tumorigenesis. The p53 activity is related to the induction of apoptosis, while the stimulation of NF-κB promotes resistance to apoptosis [152]. Various NF-κB antagonists are currently developed to suppress the beta-activity of IκB kinase (IKK) in lung cancer [153]. Accumulated evidence indicates the involvement of NF-κB (the p65 subunit of NF-κB) in acute lung injury [154]. The NF-κB pathway contributes to the pathogenesis of asthma. The pathway plays an important role in mucus overproduction and airway remodeling processes [108]. NF-kB activation implicates TLR signaling cascades that control the synthesis of proinflammatory cytokines and pro-allergic mediators

(TSLP, IL-25, IL-33), enhancing the Th2-mediated immune response [155]. NF-κB expression is significantly increased in patients with severe asthma; therefore, many drugs used in asthma therapy inhibit inflammatory reactions in the airways through inactivating the NF-κB pathway [156, 157].

Activating protein 1

Activating protein 1 (AP-1) is a key transcription factor that regulates a wide range of cellular processes, including apoptosis, differentiation, migration, and transformation of cells, and is also involved in the expression of cytokine genes [158]. Four subtypes of the protein were identified: Jun (v-Jun, c-Jun, JunB, and JunD), Fos (v-Fos, c-Fos, FosB, Fral, and Fra2), ATF (ATF2, ATF3/LRF1, B-ATF, JDP1, and JDP2) and MAF (c-Maf, MafB, MafA, MafG/F/K, and Nrl). These subtypes are capable of forming dimers. Despite high degree of structural homology, dimers differ in their capability to activate or suppress gene expression, which suggests their specific regulatory functions. Various methyltransferases regulate the activity of AP-1 in different ways [158]. AP-1 activity is induced by physiological and environmental stimuli (growth factors, neurotransmitters, polypeptide hormones, cytokines, UV exposure, bacterial and viral infections). Increased AP-1 expression was detected in the airways of asthma patients. Fos-associated antigen 2 (Fra-2) belongs to the AP-1 family and is involved in different aspects of cell functioning. The surge of Fra-2 expression was described in several chronic lung diseases, in particular, asthma. High levels of Fra-2 expression trigger inflammation associated with remodeling of the parenchyma and vasculature, which leads to fibrosis and pulmonary hypertension [159].

The relationships between eicosanoids, pro-resolving lipid mediators, endocannabinoids and nuclear transcription factors (PPARs, GR, AP-1, NF-kB) in asthma

The imbalance between anti-inflammatory and proinflammatory nuclear transcription factors plays an important role in the response to treatment [35, 143]. As mentioned above, asthma therapy includes inhaled β2-AR agonists, inhaled and systemic GCs, LTSIs and LTRAs [15]. Resistance to GCs in patients with severe asthma remains a serious clinical problem [16-18, 160]. GC resistance depends on the expression and affinity of GR, as well as many intracellular mediators controlling the signal transduction pathway [149, 161]. The anti-inflammatory effect of GCs is implemented via GR that suppresses the activity of proinflammatory NF-kB and AP-1 (this mechanism is known as *transrepression*) [162]. This results in the inhibition of the inflammatory response in the bronchopulmonary system. It should be noted that different way of implementing the anti-inflammatory action of GCs is PPAR activation [163]. Despite efforts of the pharmaceutical and academic communities, the search for selective GR modulators with potent anti-inflammatory or anticancer properties, but with fewer side effects, has had so far a somewhat limited success [164]. Several selective GR agonists are currently in preclinical development, but only three of them (GW870086X, AZD5423, AZD7594) have potential therapeutic value for asthma treatment and are in clinical trials [165].

Asthma is characterized by the imbalance between anti-inflammatory (GR, PPARs) and proinflammatory (AP-1, NF-κB) nuclear transcription factors [35, 143]. The resolution of acute inflammation is the process of switching the synthesis of proinflammatory lipid mediators to the formation of SPMs [28]. It is known that proinflammatory stimuli activate NF-κB, AP-1 and promote the synthesis of eicosanoids (PGD2 and PGE2), triggering PPARs (PPARα and PPARγ). Activated PPARs, in turn, inhibit NF-κB activity, which leads to the suppression of inflammation. Possible mechanisms of NF-kB inactivation include not only direct binding of NF-kB to PPARs, but also the indirect effect of PPARs via stimulating the production of antioxidant enzymes and reducing the concentration of reactive oxygen species. The endocannabinoid system is also involved in this process since endocannabinoids are agonists for several subtypes of PPARs [39, 40]. Pro-resolving lipid mediators also exert anti-inflammatory and cytoprotective effects through their interaction with PPARs, GRs and blockade of NF-κB [58, 25]. According to S. Muralikumar et al., the highest activity of FAs and their derivatives as PPARγ agonists is characteristic in a decreasing order for RvE1, PD1, DHA, EPA, and LXA4 [166].

The pathways of the balance regulation between proinflammatory and anti-inflammatory nuclear transcription factors by lipid metabolites of ω-3 and ω-6 PUFAs are currently actively studied [19, 24, 25]. These receptors are expressed by cells of the bronchopulmonary system and play an important role in its immunometabolic homeostasis.

It is known that ω-3 and ω-6 PUFAs are precursors for the synthesis of SPMs [24, 25] and endocannabinoids [26]. There is evidence that ω-6 PUFAs and their oxidized form can lead to the development of resistance to GCSs in asthma patients through the increase in NF-kB expression and the decrease in GR activity [38]. At the same time, the metabolite of linoleic acid also causes resistance to GCSs [38]. Therefore, maintaining a balance between ω-3 and ω-6 PUFAs allows reducing inflammation in the bronchopulmonary system by stimulating the production of SPMs. Hence, this mechanism can be one of the goals in overcoming the resistance to GCSs in asthma [42]. PUFAs are of considerable interest as modulators of chronic inflammation in asthma. The study of the effect of PUFA-containing supplements on the production of SPMs, which are agonists of PPARs, opens up new opportunities in the development of an effective therapeutic strategy for asthma via correcting the resolution of inflammation rather than suppressing its onset and development [29].

Epidemiological and clinical studies on the effectiveness of using ω-3 PUFAs in asthma

Recent changes in the diet leading to a low ratio of ω-3 and ω-6 PUFAs contribute to the exacerbation of asthma [46, 167]. Therefore, ω-3 PUFA supplementation (primarily, supplements containing pure EPA, DHA, or their combination) is proposed as the supportive treatment for this pathology [44]. It is believed that ω-3 PUFAs play an anti-inflammatory role by competing with the arachidonic acid cascade to attenuate the action of proinflammatory eicosanoids (PGs and LTs) or by its converting to potent SPMs [47]. Eosinophils play an essential role in allergic inflammatory diseases and asthma due to their ability to produce CysLT. Its biosynthesis is important as a proallergic mechanism. However, eosinophils synthesize SPMs from DHA and AA, which implied their regulatory role in inflammation [168]. Therefore, the impairment of PUFA metabolism in eosinophils may be an important component in asthma pathogenesis.

Intake of ω-3 PUFAs is more effective for reducing IL-17A in asthma patients than sublingual immunotherapy, while both methods are effective according to indicators of asthma control

test (ACT), peak expiratory flow rate (PEFR), and forced expiratory volume in the first second (FEV1) [45]. It was shown that the EPA/DHA ratio is higher in controlled or partially controlled asthma, compared with uncontrolled asthma [169]. Patients with a high ratio required inhaled corticosteroids less than patients with a low ratio. This study suggests that a higher level of ω-3 PUFAs plays an important role in the response of asthma patients to the treatment [169]. The EPA intake is associated with a decrease in the number of eosinophils in the airways and the downregulation of the expression of inflammatory mediators in the lungs. Intravenous administration of 12-hydroxy-17,18-epoxyeicosatetraenoic acid (12-OH-17,18-EpETE), an EPA metabolite, attenuate eosinophilic airway inflammation [170]. At the same time, DHA is more effective for modulating cardiometabolic risk factors [171]. In contrast to the use of EPA, the combination of EPA and DHA significantly improves the clinical course of asthma (decreased airway hyperresponsiveness, eosinophilic inflammation, and levels of inflammatory cytokines (IL-5, IFN-γ, and IL-6). The combined use of EPA and DHA was confirmed to reduce an airway inflammation by promoting the production of pro-resolving lipid mediators RvD1 and RvD4 [172]. When using particular FAs as therapeutic agents in asthma, their different effects should be taken into account.

Despite positive results of using ω-3 PUFAs in asthma therapy, the EPIC (European Prospective Investigation into Cancer and Nutrition Heidelberg cohort) study did not reveal their therapeutic effect [173]. The combined ω-3 and ω-6 PUFA supplementation at a dose of 1.19 g/day did not cause a bronchoprotective and anti-inflammatory effect in patients with exercise-induced asthma [174].

There is limited evidence for the benefits of ω-3 PUFAs in reducing the risk of allergic diseases and asthma in childhood [175]. It is thought that atopic sensitization can be prevented by eating fish during pregnancy, infancy, and childhood [176]. In children with the common variant of FADS, the high intake of EPA and DHA from fish diet during childhood is closely related to the low risk of asthma incidence before the middle adolescence [48]. According to other data, the consumption of fish and FAs during pregnancy is associated with the development of asthma in their children [177]. In a recent review, Y. Zhang et al. analyzed data on the effect of ω-3 PUFAs on the course of allergic diseases in childhood, using the PubMed, EMBASE, and international trial registers of the Cochrane Central Register of Controlled Trials (ClinicalTrials.gov and ISRCTN Registry) up to 2018. The evidence from meta-analysis-based studies demonstrated that ω-3 PUFAs did not significantly alter the risk of atopy and eczema [49]. Another study presented the results of randomized controlled trials evaluating the effect of ω-3 PUFA intake during pregnancy on the incidence of asthma in children, based on publications from the PubMed, Embase and Central databases up to 2017 [50]. Interestingly, the consumption of ω-3 PUFAs during pregnancy reduces the incidence of asthma in children, but not the incidence of asthma in pregnant women. I. Trambusti et al. summarized data on the potential role of prenatal and perinatal dietary and nutritional interventions in the primary prevention of asthma in children [43]. The authors suggested that further research is needed to elucidate the strategies of primary prevention of childhood asthma.

Consumption of ω-3 PUFAs is associated with an anti-inflammatory effect [178, 179]. G. Piazzi et al. discovered that the dietary fats (eicosapentaenoic acid-free fatty acid) led to a switch from ω-6 to ω-3 PUFAs and a reduction in PGE2 production [180]. However, PUFAs are susceptible to oxidation, which is accompanied by the formation of proinflammatory mediators [44]. A.M. Corteselli et al. studied the effect of tropospheric ozone (O_3) on the development of oxidative stress in human airway epithelial cells when taking ω-3 PUFAs [44]. The increased formation of lipid hydroperoxides as a result of the reaction of O_3 with PUFAs was confirmed [44]. Given the proinflammatory activity of lipid hydroperoxides, further study of the potential role of ω-3 PUFAs in increasing human susceptibility to adverse health effects of O_3 is needed.

The lack of standardized doses significantly limits the use of ω-3 PUFAs as well [21]. Remarkably, both high (6.2 g/day [3.7 g EPA and 2.5 g DHA]) and low doses (3.1 g/day [1.8 g EPA and 1.3 g DHA]) of ω-3 PUFAs equally enfeebled bronchospasm and reduced the levels of airway inflammation markers [178].

The effect of SPMs in vivo is just beginning to be studied. A number of studies proposed a promising approach to personalized therapy of inflammation-related diseases by using ω-3 PUFA derivates [96]. RvE1 is known to reduce airway sensitivity and inflammation in asthmatic mice. Although ω-3 PUFAs are precursors of RvE1, it was demonstrated that they have no effect on RvE1 levels in airway inflammation and reactive airway disease. Therefore, ω-3 PUFA supplementation insignificantly affects airway inflammation and reactive airway disease [114]. The inconsistency of the available data suggests the prospects for further study of this issue.

Conclusion

Inflammation is an acute response of tissues and systems to traumatic or stressful influences. The resolution of inflammation is known as a controlled termination program of the inflammatory response. It is assumed that chronic inflammation in the lungs may be the result of a defect in the resolution of the inflammatory process, viz., the functional imbalance between eicosanoids, endogenous specialized pro-resolving lipid mediators and endocannabinoids. The precursors for the formation of lipid mediators are PUFAs. Resolvins, protectins and maresins are synthesized from ω-3 PUFAs; eicosanoids, lipoxins, endocannabinoids are derived from ω-6 PUFAs. All lipid mediators directly (through membrane receptors, intracellular nuclear transcription factors) or indirectly interact with each other, thereby forming a single metabolic network that controls the inflammatory response. It has been established that SPMs are PPARs and GR agonists. The anti-inflammatory effect of these receptors is to suppress the activity of proinflammatory transcriptional nuclear factors, NF-kB and AP-1.

Conflict of interest

We declare that we have no conflicts of interest.

Funding

Our project was funded from the federal budget of the Russian Federation.

References

1. Holguin F, Cardet JC, Chung KF, Diver S, Ferreira DS, Fitzpatrick A, et al. Management of severe asthma: a European Respiratory

Society/American Thoracic Society guideline. *Eur Respir J* 2020; 55(1): 1900588. https://doi.org/10.1183/13993003.00588-2019.

2. Mauer Y, Taliercio RM. Managing adult asthma: The 2019 GINA guidelines. *Cleve Clin J Med* 2020; 87(9): 569-575. https://doi.org/10.3949/ccjm.87a.19136.
3. Mandlik DS, Mandlik SK. New perspectives in bronchial asthma: Pathological, immunological alterations, biological targets, and pharmacotherapy. *Immunopharmacol Immunotoxicol* 2020; 42(6): 521-544. https://doi.org/10.1080/08923973.2020.1824238.
4. Hamilton D, Lehman H. Asthma Phenotypes as a guide for current and future biologic therapies. *Clin Rev Allergy Immunol* 2020 Oct;59(2):160-174. https://doi.org/10.1007/s12016-019-08760-x.
5. Conrad LA, Cabana MD, Rastogi D. Defining pediatric asthma: Phenotypes to endotypes and beyond. *Pediatr Res* 2021; 90(1): 45-51. https://doi.org/10.1038/s41390-020-01231-6.
6. Berdine G, Alexander R, Nugent K. Clinical entities, phenotypes, causation, and endotypes based on selected asthma publications. *Proc (Bayl Univ Med Cent)* 2020; 33(4): 580-585. https://doi.org/10.1080/08998280.2020.1793444.
7. Global Initiative for Asthma. (GINA). Global Strategy for Asthma Management and Prevention. 2021; 217 p. https://ginasthma.org/wp-content/uploads/2021/05/GINA-Main-Report-2021-V2-WMS.pdf.
8. Wangberg H, Woessner K. Choice of biologics in asthma endotypes. *Curr Opin Allergy Clin Immunol* 2021; 21(1): 79-85. https://doi.org/10.1097/aci.0000000000000708.
9. Chan R, RuiWen Kuo C, Lipworth B. Pragmatic Clinical Perspective on Biologics for Severe Refractory Type 2 Asthma. J *Allergy Clin Immunol Pract* 2020; 8(10): 3363-3370. https://doi.org/10.1016/j.jaip.2020.06.048.
10. Berghi NO, Dumitru M, Vrinceanu D, Ciuluvica RC, Simioniuc-Petrescu A, Caragheorgheopol R, et al. Relationship between chemokines and T lymphocytes in the context of respiratory allergies (Review). *Exp Ther Med* 2020; 20(3): 2352-2360 https://doi.org/10.3892/etm.2020.8961.
11. Nabe T. Steroid-resistant asthma and neutrophils. *Biol Pharm Bull* 2020; 43(1): 31-35. https://doi.org/10.1248/bpb.b19-00095.
12. Domvri K, Porpodis K, Tzimagiorgis G, Chatzopoulou F, Kontakiotis T, Kyriazis G, et al. Th2/Th17 cytokine profile in phenotyped Greek asthmatics and relationship to biomarkers of inflammation. *Respir Med* 2019; 151: 102-110. https://doi.org/10.1016/j.rmed.2019.03.017.
13. Boonpiyathad T, Sözener ZC, Satitsuksanoa P, Akdis CA. Immunologic mechanisms in asthma. *Semin Immunol* 2019; 46: 101333. https://doi.org/10.1016/j.smim.2019.101333.
14. GBD 2019 Diseases and Injuries Collaborators. Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet 2020; 396(10258): 1204-1222 https://doi.org/10.1016/s0140-6736(20)30925-9.
15. Jenkins CR, Bateman ED, Sears MR, O'Byrne PM. What have we learnt about asthma control from trials of budesonide/formoterol as maintenance and reliever? *Respirology* 2020; 25(8): 804-815. https://doi.org/10.1111/resp.13804.
16. Agache I, Akdis CA, Akdis M, Canonica GW, Casale T, Chivato T, et al. EAACI Biologicals Guidelines– Recommendations for severe asthma. *Allergy* 2021; 76(1): 14-44. https://doi.org/10.1111/all.14425.
17. Pelaia C, Crimi C, Vatrella A, Tinello C, Terracciano R, Pelaia G. Molecular Targets for Biological Therapies of Severe Asthma. *Front Immunol* 2020; 11: 603312. https://doi.org/10.3389/fimmu.2020.603312.
18. Kytikova OY, Novgorodtseva TP, Denisenko YK, Antonyuk MV, Gvozdenko TA. Dysfunction of transient receptor potential ion channels as an important pathophysiological mechanism in asthma *Russ Open Med J* 2020; 9: e0102. https://doi.org/10.15275/rusomj.2020.0102.
19. Bayani A, Dunster JL, Crofts JJ, Nelson MR. Mechanisms and points of control in the spread of inflammation: A mathematical investigation. *Bull Math Biol* 2020; 82(4): 45. https://doi.org/10.1007/s11538-020-00709-y.
20. Yang A, Wu Y, Yu G, Wang H. Role of specialized pro-resolving lipid mediators in pulmonary inflammation diseases: Mechanisms and development. *Respir Res* 2021; 22(1): 204. https://doi.org/10.1186/s12931-021-01792-y.
21. Venter C, Meyer RW, Nwaru BI, Roduit C, Untersmayr E, Adel-Patient K, et al. EAACI position paper: Influence of dietary fatty acids on asthma, food allergy, and atopic dermatitis. *Allergy* 2019; 74(8): 1429-1444. https://doi.org/10.1111/all.13764.
22. Zhu Z, Camargo CA Jr, Hasegawa K. Metabolomics in the prevention and management of asthma. *Expert Rev Respir Med* 2019; 13(12): 1135-1138. https://doi.org/10.1080/17476348.2019.1674650.
23. Kytikova OY, Novgorodtseva TP, Denisenko YK, Antonyuk MV, Gvozdenko TA. Medium and long chain free fatty acid receptors in the pathophysiology of respiratory diseases. *Bulletin Physiology and Pathology of Respiration* 2021; (80): 115-128. Russian. https://doi.org/10.36604/1998-5029-2021-80-115-128.
24. Das UN. Bioactive lipids in age-related disorders. *Adv Exp Med Biol* 2020; 1260: 33-83. https://doi.org/10.1007/978-3-030-42667-5_3.
25. Margină D, Ungurianu A, Purdel C, Nitulescu GM, Tsoukalas D, Sarandi E, et al. Analysis of the intricate effects of polyunsaturated fatty acids and polyphenols on inflammatory pathways in health and disease. *Food Chem Toxicol* 2020; 143: 111558. https://doi.org/10.1016/j.fct.2020.111558.
26. Fisk HL, Childs CE, Miles EA, Ayres R, Noakes PS, Paras-Chavez C, et al. Dysregulation of endocannabinoid concentrations in human subcutaneous adipose tissue in obesity and modulation by omega-3 polyunsaturated fatty acids. *Clin Sci (Lond)* 2021; 135(1): 185-200. https://doi.org/10.1042/CS20201060.
27. Lu HC, Mackie K. Review of the endocannabinoid system. *Biol Psychiatry Cogn Neurosci Neuroimaging* 2021; 6(6): 607-615. https://doi.org/10.1016/j.bpsc.2020.07.016.
28. Kilaru A, Chapman KD. The endocannabinoid system. *Essays Biochem* 2020; 64(3): 485-499. https://doi.org/10.1042/EBC20190086.
29. Kytikova OY, Novgorodtseva TP, Antonyuk MV, Denisenko YK, Gvozdenko TA. Pro-resolving lipid mediators in the pathophysiology of asthma. *Medicina (Kaunas)* 2019; 55(6): 284. https://doi.org/10.3390/medicina55060284.
30. Yonker LM, Barrios J, Mou H, Hurley BP. Untapped potential: Therapeutically targeting eicosanoids and endocannabinoids in the lung. *Clin Pharmacol Ther* 2021; 110(1): 69-81. https://doi.org/10.1002/cpt.2165.
31. Chiang N, Serhan CN. Specialized pro-resolving mediator network: An update on production and actions. *Essays Biochem* 2020; 64(3): 443-462. https://doi.org/10.1042/EBC20200018.
32. Serhan CN, Gupta SK, Perretti M, Godson C, Brennan E, Li Y, et al. The Atlas of Inflammation Resolution (AIR). *Mol Aspects Med* 2020: 74: 100894. https://doi.org/10.1016/j.mam.2020.100894.
33. Panigrahy D, Gilligan MM, Serhan CN, Kashfi K. Resolution of inflammation: An organizing principle in biology and medicine. *Pharmacol Ther* 2021; 227: 107879. https://doi.org/10.1016/j.pharmthera.2021.107879.
34. Serhan CN, Levy BD. Resolvins in inflammation: Emergence of the pro-resolving superfamily of mediators. J Clin Invest 2018; 128(7): 2657-2669. https://doi.org/10.1172/JCI97943.
35. Kytikova OY, Novgorodtseva TP, Antonyuk MV, Gvozdenko TA. Peroxisome proliferator-activated receptors as a therapeutic target in asthma. *PPAR Res* 2020; 2020: 8906968. https://doi.org/10.1155/2020/8906968.
36. Christofides A, Konstantinidou E, Jani C, Boussiotis VA. The role of peroxisome proliferator-activated receptors (PPAR) in immune responses. *Metabolism* 2021; 114:154338. https://doi.org/10.1016/j.metabol.2020.154338.

37. Zhang T, Dai Y, Zhang L, Tian Y, Li Z, Wang J. Effects of edible oils with different n-6/n-3 PUFA ratios on articular cartilage degeneration via regulating the NF-kappa B signaling pathway. *J Agric Food Chem* 2020; 68(45): 12641-12650. https://doi.org/10.1021/acs.jafc.0c05240.
38. Panda L, Gheware A, Rehman R, Yadav MK, Jayaraj BS, Madhunapantula SV, et al. Linoleic acid metabolite leads to steroid resistant asthma features partially through NF-kB. *Sci Rep* 2017; 7(1): 9565. https://doi.org/10.1038/s41598-017-09869-9.
39. Brunetti L, Carrieri A, Piemontese L, Tortorella P, Loiodice F, Laghezza A. Beyond the Canonical Endocannabinoid System. A screening of PPAR ligands as FAAH inhibitors. *Int J Mol Sci* 2020; 21(19): 7026. https://doi.org/10.3390/ijms21197026.
40. Karwad MA, Couch DG, Wright KL, Tufarelli C, Larvin M, Lund J, O'Sullivan SE. Endocannabinoids and endocannabinoid-like compounds modulate hypoxia-induced permeability in CaCo-2 cells via CB (1), TRPV1, and PPARalpha. *Biochem Pharmacol* 2019; 168: 465-472. https://doi.org/10.1016/j.bcp.2019.07.017.
41. Petrosino S, Di Marzo V. The pharmacology of palmitoylethanolamide and first data on the therapeutic efficacy of some of its new formulations. *Br J Pharmacol* 2017; 174(11): 1349-1365. https://doi.org/10.1111/bph.13580.
42. Livshits G, Kalinkovich A. Receptors for pro-resolving mediators as a therapeutic tool for smooth muscle remodeling-associated disorders. *Pharmacol Res* 2021; 164: 105340. https://doi.org/10.1016/j.phrs.2020.105340.
43. Trambusti I, Nuzzi G, Costagliola G, Verduci E, D'Auria E, Peroni DG, et al. Dietary interventions and nutritional factors in the prevention of pediatric asthma. *Front Pediatr* 2020; 8: 480. https://doi.org/10.3389/fped.2020.00480.
44. Corteselli EM, Gold A, Surratt J, Cui T, Bromberg P, Dailey L, et al. Supplementation with omega-3 fatty acids potentiates oxidative stress in human airway epithelial cells exposed to ozone. *Environ Res* 2020; 187:1 09627. https://doi.org/10.1016/j.envres.2020.109627.
45. Abdo-Sultan MK, Abd-El-Lateef RS, Kamel FZ. Efficacy of omega-3 fatty acids supplementation versus sublingual immunotherapy in patients with bronchial asthma. *Egypt J Immunol* 2019; 26(1): 79-89. https://pubmed.ncbi.nlm.nih.gov/31332998.
46. Oliver PJ, Arutla S, Yenigalla A, Hund TJ, Parinandi NL. Lipid Nutrition in Asthma. *Cell Biochem Biophys* 2021; 79(3): 669-694. https://doi.org/10.1007/s12013-021-01020-w.
47. D'Auria E, Peroni DG, Sartorio MUA, Verduci E, Zuccotti GV, Venter C. The role of diet diversity and diet indices on allergy outcomes. *Front Pediatr* 2020; 8: 545. https://doi.org/10.3389/fped.2020.00545.
48. Talaei M, Sdona E, Calder PC, Jones LR, Emmett PM, Granell R, et al. Intake of n-3 polyunsaturated fatty acids in childhood, FADS genotype, and incident asthma. *Eur Respir J* 2021; 58(3): 2003633. https://doi.org/10.1183/13993003.03633-2020.
49. Zhang Y, Lin J, Zhou R, Zheng X, Dai J. Effect of omega-3 fatty acids supplementation during childhood in preventing allergic disease: A systematic review and meta-analysis. *J Asthma* 2021; 58(4): 523-536. https://doi.org/10.1080/02770903.2019.1709866.
50. Lin J, Zhang Y, Zhu X, Wang D, Dai J. Effects of supplementation with omega-3 fatty acids during pregnancy on asthma or wheeze of children: A systematic review and meta-analysis. *J Matern Fetal Neonatal Med* 2020; 33(10): 1792-1801. https://doi.org/10.1080/14767058.2018.1529161.
51. Schulze MB, Minihane AM, Saleh RNM, Risérus U. Intake and metabolism of omega-3 and omega-6 polyunsaturated fatty acids: Nutritional implications for cardiometabolic diseases. *Lancet Diabetes Endocrinol* 2020; 8(11): 915-930. https://doi.org/10.1016/S2213-8587(20)30148-0.
52. Elagizi A, Lavie CJ, O'Keefe E, Marshall K, O'Keefe JH, Milani RV. An Update on omega-3 polyunsaturated fatty acids and cardiovascular health. *Nutrients* 2021; 13(1): 204. https://doi.org/10.3390/nu13010204.
53. Saini RK, Keum YS. Omega-3 and omega-6 polyunsaturated fatty acids: Dietary sources, metabolism, and significance – A review. *Life Sci* 2018; 203: 255-267. https://doi.org/10.1016/j.lfs.2018.04.049.
54. Shramko VS, Polonskaya YV, Kashtanova EV, Stakhneva EM, Ragino YI. The short overview on the relevance of fatty acids for human cardiovascular disorders. *Biomolecules* 2020; 10(8): 1127. https://doi.org/10.3390/biom10081127.
55. Tanno H, Sassa T, Sawai M, Kihara A. Production of branched-chain very-long-chain fatty acids by fatty acid elongases and their tissue distribution in mammals. *Biochim Biophys Acta Mol Cell Biol Lipids* 2021; 1866(1): 158842. https://doi.org/10.1016/j.bbalip.2020.158842.
56. Nie L, Pascoa TC, Pike ACW, Bushell SR, Quigley A, Ruda GF, et al. The structural basis of fatty acid elongation by the ELOVL elongases. *Nat Struct Mol Biol* 2021; 28(6): 512-520. https://doi.org/10.1038/s41594-021-00605-6.
57. Peng Z, Chang Y, Fan J, Ji W, Su C. Phospholipase A2 superfamily in cancer. *Cancer Lett* 2021; 497: 165-177. https://doi.org/10.1016/j.canlet.2020.10.021.
58. Calder PC. Eicosanoids. *Essays Biochem* 2020; 64(3): 423-441. https://doi.org/10.1042/EBC20190083.
59. Sarparast M, Dattmore D, Alan J, Lee KSS. Cytochrome P450 metabolism of polyunsaturated fatty acids and neurodegeneration. *Nutrients* 2020; 12(11): 3523. https://doi.org/10.3390/nu12113523.
60. Wasserman, AH, Venkatesan M, Aguirre A. Bioactive lipid signaling in cardiovascular disease, development, and regeneration. *Cells* 2020; 9(6): 1391. https://doi.org/10.3390/cells9061391.
61. Al-Azzam N, Elsalem L. Leukotriene D(4) role in allergic asthma pathogenesis from cellular and therapeutic perspectives. *Life Sci* 2020; 260: 118452. https://doi.org/10.1016/j.lfs.2020.118452.
62. Kolmert J, Gómez C, Balgoma D, Sjödin M, Bood J, Konradsen JR, et al. U-BIOPRED Study Group, on behalf of the U-BIOPRED Study Group. Urinary leukotriene E(4) and prostaglandin D(2) metabolites increase in adult and childhood severe asthma characterized by type 2 inflammation. A clinical observational study. *Am J Respir Crit Care Med* 2021; 203(1): 37-53. https://doi.org/10.1164/rccm.201909-1869OC.
63. Imig JD. Eicosanoid blood vessel regulation in physiological and pathological states. *Clin Sci (Lond)* 2020; 134(20): 2707-2727. https://doi.org/10.1042/CS20191209.
64. Gonzalez-Fernandez E, Staursky D, Lucas K, Nguyen BV, Li M, Liu Y, et al. 20-HETE enzymes and receptors in the neurovascular unit: Implications in cerebrovascular disease. *Front Neurol* 2020; 11: 983. https://doi.org/10.3389/fneur.2020.00983.
65. Chen LC, Tseng HM, Kuo ML, Chiu CY, Liao SL, Su KW, et al. Levels of 15-HETE and TXB_2 in exhaled breath condensates as markers for diagnosis of childhood asthma and its therapeutic outcome. *Pediatr Allergy Immunol* 2021; 32(8): 1673-1680. https://doi.org/10.1111/pai.13587.
66. Pascale JV, Park EJ, Adebesin AM, Falck JR, Schwartzman ML, Garcia V. Uncovering the signalling, structure and function of the 20-HETE-GPR75 pairing: Identifying the chemokine CCL5 as a negative regulator of GPR75. *Br J Pharmacol* 2021; 178(18): 3813-3828. https://doi.org/10.1111/bph.15525.
67. Olivares-Rubio HF, Espinosa-Aguirre JJ. Role of epoxyeicosatrienoic acids in the lung. *Prostaglandins Other Lipid Mediat* 2020; 149: 106451. https://doi.org/10.1016/j.prostaglandins.2020.106451.
68. Zuo D, Pi Q, Shi Y, Luo S, Xia Y. Dihydroxyeicosatrienoic acid, a metabolite of epoxyeicosatrienoic acids upregulates endothelial nitric oxide synthase expression through transcription: Mechanism of vascular endothelial function protection. *Cell Biochem Biophys* 2021; 79(2): 289-299. https://doi.org/10.1007/s12013-021-00978-x.
69. Li Y, Deng SL, Lian ZX et al. Roles of Toll-Like Receptors in Nitroxidative Stress in Mammals. *Cells* 2019; 8(6): 576. https://doi.org/10.3390/cells806.

70. Wangberg H, White AA. Aspirin-exacerbated respiratory disease. *Curr Opin Immunol* 2020; 66: 9-13. https://doi.org/10.1016/j.coi.2020.02.006.
71. Liu T, Barrett NA, Nagai J, Lai J, Feng C, Boyce JA. Leukotriene D4 paradoxically limits LTC4-driven platelet activation and lung immunopathology. *J Allergy Clin Immunol* 2021; 148(1): 195-208.e5. https://doi.org/10.1016/j.jaci.2020.10.041.
72. Dholia N, Sethi GS, Naura AS, Yadav UCS. Cysteinyl leukotriene D4 (LTD4) promotes airway epithelial cell inflammation and remodelling. *Inflamm Res* 2021; 70(1): 109-126. https://doi.org/10.1007/s00011-020-01416-z.
73. Lau KE, Lui F. Physiology, Prostaglandin I2. 2022. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing. 2023. https://pubmed.ncbi.nlm.nih.gov/32965944.
74. Feng X, Zhang Y, Zhang Y, Yang X, Man D, Lu L, et al. Prostaglandin I2 mediates weak vasodilatation in human placental microvessels. *Biol Reprod* 2020; 103(6): 1229-1237. https://doi.org/10.1093/biolre/ioaa156.
75. Norel X, Sugimoto Y, Ozen G, Abdelazeem H, Amgoud Y, Bouhadoun A, et al. International Union of Basic and Clinical Pharmacology. CIX. Differences and similarities between human and rodent prostaglandin E_2 receptors (EP1-4) and prostacyclin receptor (IP): Specific roles in pathophysiologic conditions. *Pharmacol Rev* 2020; 72(4): 910-968. https://doi.org/10.1124/pr.120.019331.
76. Peng L, Ye Y, Mullikin H, Lin L, Kuhn C, Rahmeh M, et al. Expression of trophoblast derived prostaglandin E2 receptor 2 (EP2) is reduced in patients with recurrent miscarriage and EP2 regulates cell proliferation and expression of inflammatory cytokines. *J Reprod Immunol* 2020; 142: 103210. https://doi.org/10.1016/j.jri.2020.103210.
77. Diao G, Huang J, Zheng X, Sun X, Tian M, Han J, et al. Prostaglandin E2 serves a dual role in regulating the migration of dendritic cells. *Int J Mol Med* 2021; 47(1): 207-218. https://doi.org/10.3892/ijmm.2020.4801.
78. Gao X, Zhuang J, Zhao L, Wei W, Xu F. Cross-effect of TRPV1 and EP3 receptor on coughs and bronchopulmonary C-neural activities. *PLoS One* 2021; 16(2): e0246375. https://doi.org/10.1371/journal.pone.0246375.
79. Ohyama K, Sugiura M. Evaluation of the association between topical prostaglandin $f_{2\alpha}$ analogs and asthma using the JADER database: Comparison with β-blockers. *Yakugaku Zasshi* 2018; 138(4): 559-564. https://doi.org/10.1248/yakushi.17-00162.
80. Maehara T, Higashitarumi F, Kondo R, Fujimori K. Prostaglandin $F_{2\alpha}$ receptor antagonist attenuates LPS-induced systemic inflammatory response in mice. *FASEB J* 2020; 34(11): 15197-15207. https://doi.org/10.1096/fj.202001481R.
81. Siripornpanich S, Chongviriyaphan N, Manuyakorn W, Matangkasombut P. Zinc and vitamin C deficiencies associate with poor pulmonary function in children with persistent asthma. *Asian Pac J Allergy Immunol* 2020; 40(2): 103-110. https://doi.org/10.12932/AP-100620-0878.
82. Xia J, Abdu S, Maguire TJA, Hopkins C, Till SJ, Woszczek G. Prostaglandin D_2 receptors in human mast cells. *Allergy* 2020; 75(6): 1477-1480. https://doi.org/10.1111/all.14161.
83. Brightling CE, Brusselle G, Altman P. The impact of the prostaglandin D_2 receptor 2 and its downstream effects on the pathophysiology of asthma. *Allergy* 2020; 75(4): 761-768. https://doi.org/10.1111/all.14001.
84. Kerstjens HAM, Gosens R. Prostaglandin D_2: The end of a story or just the beginning? *Lancet Respir Med* 2021; 9(1): 2-3. https://doi.org/10.1016/S2213-2600(20)30449-5.
85. Takemura M, Niimi A, Matsumoto H, Ueda T, Yamaguchi M, Matsuoka H, et al. Imbalance of endogenous prostanoids in moderate-to-severe asthma. *Allergol Int* 2017; 66(1): 83-88. https://doi.org/10.1016/j.alit.2016.05.013.
86. Uchida Y, Soma T, Nakagome K, Kobayashi T, Nagata M. Implications of prostaglandin D2 and leukotrienes in exhaled breath condensates of asthma. *Ann Allergy Asthma Immunol* 2019; 123(1): 81-88.e1. https://doi.org/10.1016/j.anai.2019.04.008.
87. Lee K, Lee SH, Kim TH. The biology of prostaglandins and their role as a target for allergic airway disease therapy. *Int J Mol Sci* 2020; 21(5): 1851. https://doi.org/10.3390/ijms21051851.
88. Rucker D, Dhamoon AS. Physiology, Thromboxane A2. 2022 Sep 13. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing. 2023. https://pubmed.ncbi.nlm.nih.gov/30969639.
89. Braune S, Küpper JH, Jung F. Effect of prostanoids on human platelet function: An overview. *Int J Mol Sci* 2020; 21(23): 9020. https://doi.org/10.3390/ijms21239020.
90. Johnsson AK, Choi JH, Rönnberg E, Fuchs D, Kolmert J, Hamberg M, et al. Selective inhibition of prostaglandin D2 biosynthesis in human mast cells to overcome need for multiple receptor antagonists: Biochemical consequences. *Clin Exp Allergy* 2021; 51(4): 594-603. https://doi.org/10.1111/cea.13831.
91. Patrono C, Rocca B. Measurement of thromboxane biosynthesis in health and disease. *Front Pharmacol* 2019; 10: 1244. https://doi.org/10.3389/fphar.2019.01244.
92. Liu L, Feng A, Du C, Qi C. Relationship between the changes in thromboxane B2, 6-keto-prostaglandin Fla, and blood glucose levels and progressive ischemic stroke. *Ann Palliat Med* 2021; 10(5): 5373-5379. https://doi.org/10.21037/apm-21-774.
93. Chen LC, Tseng HM, Kuo ML, Chiu CY, Liao SL, Su KW, et al. Levels of 15-HETE and TXB_2 in exhaled breath condensates as markers for diagnosis of childhood asthma and its therapeutic outcome. *Pediatr Allergy Immunol* 2021; 32(8): 1673-1680. https://doi.org/10.1111/pai.13587.
94. Luu Quoc Q, Moon JY, Lee DH, Ban GY, Kim SH, Park HS. Role of thymus and activation-regulated chemokine in allergic asthma. *J Asthma Allergy* 2022; 15: 157-167. https://doi.org/10.2147/JAA.S351720.
95. Sønderskov J, Tungen JE, Palmas F, Dalli J, Serhan CN, Stenstrøm Y, et al. Stereoselective synthesis of $MaR2_{n\text{-}3\ DPA}$. *Tetrahedron Lett* 2020; 61(7): 151510. https://doi.org/10.1016/j.tetlet.2019.151510.
96. Giacobbe J, Benoiton B, Zunszain P, Pariante CM, Borsini A. The anti-inflammatory role of omega-3 polyunsaturated fatty acids metabolites in pre-clinical models of psychiatric, neurodegenerative, and neurological disorders. *Front Psychiatry* 2020; 11: 122. https://doi.org/10.3389/fpsyt.2020.00122.
97. Sekheri M, El Kebir D, Edner N, Filep JG. 15-Epi-LXA4 and 17-epi-RvD1 restore TLR9-mediated impaired neutrophil phagocytosis and accelerate resolution of lung inflammation. *Proc Natl Acad Sci U S A* 2020; 117(14): 7971-7980. https://doi.org/10.1073/pnas.1920193117.
98. Levy BD, Abdulnour RE, Tavares A, Brüggemann TR, Norris PC, Bai Y, et al. Cysteinyl maresins regulate the prophlogistic lung actions of cysteinyl leukotrienes. *J Allergy Clin Immunol* 2020; 145(1): 335-344. https://doi.org/10.1016/j.jaci.2019.09.028.
99. Rodriguez A.R. Spur B.W. First total synthesis of pro-resolving and tissue-regenerative resolvin sulfido-conjugates. *Tetrahedron Lett* 2017; 58: 1662-1668. https://doi.org/10.1016/j.tetlet.2017.03.041.
100. Olsen MV, Lyngstadaas AV, Bair JA, Hodges RR, Utheim TP, Serhan CN, et al. Maresin 1, a specialized proresolving mediator, stimulates intracellular $[Ca^{2+}]$ and secretion in conjunctival goblet cells. J Cell Physiol 2021; 236(1): 340-353. https://doi.org/10.1002/jcp.29846.
101. Li D, Wang M, Ye J, Zhang J, Xu Y, Wang Z, et al. Maresin 1 alleviates the inflammatory response, reduces oxidative stress and protects against cardiac injury in LPS-induced mice. *Life Sci* 2021; 277: 119467. https://doi.org/10.1016/j.lfs.2021.119467.
102. Barnig C, Frossard N, Levy BD. Towards targeting resolution pathways of airway inflammation in asthma. *Pharmacol Ther* 2018; 186: 98-113. https://doi.org/10.1016/j.pharmthera.2018.01.004.

103.Derada Troletti C, Enzmann G, Chiurchiù V, Kamermans A, Tietz SM, Norris PC, et al. Pro-resolving lipid mediator lipoxin A4 attenuates neuro-inflammation by modulating T cell responses and modifies the spinal cord lipidome. *Cell Rep* 2021; 35(9): 109201. https://doi.org/10.1016/j.celrep.2021.109201.

104.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. https://doi.org/10.3389/fimmu.2020.580598.

105.Abdolmaleki F, Kovanen PT, Mardani R, Gheibi-Hayat SM, Bo S, Sahebkar A. Resolvins: Emerging players in autoimmune and inflammatory diseases. *Clin Rev Allergy Immunol* 2020; 58(1): 82-91. https://doi.org/10.1007/s12016-019-08754-9.

106.Lamon-Fava S, So J, Mischoulon D, Ziegler TR, Dunlop BW, Kinkead B, et al. Dose- and time-dependent increase in circulating anti-inflammatory and pro-resolving lipid mediators following eicosapentaenoic acid supplementation in patients with major depressive disorder and chronic inflammation. *Prostaglandins Leukot Essent Fatty Acids* 2021; 164: 102219. https://doi.org/10.1016/j.plefa.2020.102219.

107.Ganesan R, Henkels KM, Shah K, De La Rosa X, Libreros S, Cheemarla NR, et al. D-series resolvins activate phospholipase D in phagocytes during inflammation and resolution. *FASEB J* 2020; 34(12): 15888-15906. https://doi.org/10.1096/fj.201903025RR.

108.Sun J, Huang N, Ma W, Zhou H, Lai K. Protective effects of metformin on lipopolysaccharide induced airway epithelial cell injury via NF κB signaling inhibition. *Mol Med Rep* 2019; 19(3): 1817-1823. https://doi.org/10.3892/mmr.2019.980.

109.Yang M, Bair JA, Hodges RR, Serhan CN, Dartt DA. Resolvin E1 reduces leukotriene B4-induced intracellular calcium increase and mucin secretion in rat conjunctival goblet cells. *Am J Pathol* 2020; 190(9): 1823-1832. https://doi.org/10.1016/j.ajpath.2020.06.001.

110.Libreros S, Shay AE, Nshimiyimana R, Fichtner D, Martin MJ, Wourms N, et al. A new E-series resolvin: RvE4 stereochemistry and function in efferocytosis of inflammation-resolution. *Front Immunol* 2021; 11: 631319. https://doi.org/10.3389/fimmu.2020.631319.

111.Reinertsen AF, Primdahl KG, Shay AE, Serhan CN, Hansen TV, Aursnes M. Stereoselective synthesis and structural confirmation of the specialized pro-resolving mediator resolvin E4. *J Org Chem* 2021; 86(4): 3535-3545. https://doi.org/10.1021/acs.joc.0c02913.

112.Wang M, Liu M, Zhang J, Liu J, Ye J, Xu Y, et al. Resolvin D1 protects against sepsis-induced cardiac injury in mice. *Biofactors* 2020; 46(5): 766-776. https://doi.org/10.1002/biof.1668.

113.Briottet M, Shum M, Urbach V. The Role of specialized pro-resolving mediators in cystic fibrosis airways disease. *Front Pharmacol* 2020; 11: 1290. https://doi.org/10.3389/fphar.2020.01290.

114.Siddiquee A, Patel M, Rajalingam S, Narke D, Kurade M, Ponnoth DS. Effect of omega-3 fatty acid supplementation on resolvin (RvE1)-mediated suppression of inflammation in a mouse model of asthma. *Immunopharmacol Immunotoxicol* 2019; 41(2): 250-257. https://doi.org/10.1080/08923973.2019.1584903.

115.Gagliardo R, Ferrante G, Fasola S, Di Vincenzo S, Pace E, La Grutta S. Resolvin D1 and miR-146a are independent distinctive parameters in children with moderate and severe asthma. *Clin Exp Allergy* 2021; 51(2): 350-353. https://doi.org/10.1111/cea.13771.

116.Miyata J, Yokokura Y, Moro K, Arai H, Fukunaga K, Arita M. 12/15-Lipoxygenase regulates IL-33-induced eosinophilic airway inflammation in mice. *Front Immunol* 2021; 12: 687192. https://doi.org/10.3389/fimmu.2021.687192.

117.Xia H, Ge Y, Wang F, Ming Y, Wu Z, Wang J, et al. Protectin DX ameliorates inflammation in sepsis-induced acute lung injury through mediating PPARgamma/NF-kappaB pathway. *Immunol Res* 2020; 68(5): 280-288. https://doi.org/10.1007/s12026-020-09151-7.

118.Yang JX, Li M, Hu X, Lu JC, Wang Q, Lu SY, et al. Protectin DX promotes epithelial injury repair and inhibits fibroproliferation partly via ALX/PI3K signalling pathway. *J Cell Mol Med* 2020; 24(23): 14001-14012. https://doi.org/10.1111/jcmm.16011.

119.Kasatkina LA, Rittchen S, Sturm EM. Neuroprotective and immunomodulatory action of the endocannabinoid system under neuroinflammation. *Int J Mol Sci* 2021; 22(11): 5431. https://doi.org/10.3390/ijms22115431.

120.Lal S, Shekher A, Puneet, Narula AS, Abrahamse H, Gupta SC. Cannabis and its constituents for cancer: History, biogenesis, chemistry and pharmacological activities. *Pharmacol Res* 2021; 163: 105302. https://doi.org/10.1016/j.phrs.2020.105302.

121.Aiello F, Gallo Afflitto G, Li JO, Martucci A, Cesareo M, Nucci C. CannabinEYEds: The endocannabinoid system as a regulator of the ocular surface nociception, inflammatory response, neovascularization and wound healing. *J Clin Med* 2020; 9(12): 4036. https://doi.org/10.3390/jcm9124036.

122.Ruiz de Azua I, Lutz B. Multiple endocannabinoid-mediated mechanisms in the regulation of energy homeostasis in brain and peripheral tissues. *Cell Mol Life Sci* 2019; 76(7): 1341-1363. https://doi.org/10.1007/s00018-018-2994-6.

123.Di Marzo V. New approaches and challenges to targeting the endocannabinoid system. *Nat Rev Drug Discov* 2018; 17(9): 623-639. https://doi.org/10.1038/nrd.2018.115.

124.Fields JA, Swinton MK, Montilla-Perez P, Ricciardelli E, Telese F. The Cannabinoid Receptor Agonist, WIN-55212-2, Suppresses the Activation of Proinflammatory Genes Induced by Interleukin 1 Beta in Human Astrocytes. Cannabis Cannabinoid Res. 2022; 7(1): 78-92. https://doi.org/10.1089/can.2020.0128.

125.Hillard CJ. Circulating endocannabinoids: From whence do they come and where are they going? *Neuropsychopharmacology* 2018; 43(1): 155-172. https://doi.org/10.1038/npp.2017.130.

126.Motwani MP, Bennett F, Norris PC, Maini AA, George MJ, Newson J. Potent anti-inflammatory and pro-resolving effects of anabasum in a human model of self-resolving acute inflammation. *Clin Pharmacol Ther* 2018: 104(4): 675-686. https://doi.org/10.1002/cpt.980.

127.Muller C, Morales P, Reggio PH. Cannabinoid ligands targeting TRP Channels. *Front Mol Neurosci* 2019; 11: 487. https://doi.org/10.3389/fnmol.2018.00487.

128.Lago-Fernandez A, Zarzo-Arias S, Jagerovic N, Morales P. Relevance of peroxisome proliferator activated receptors in multitarget paradigm associated with the endocannabinoid System. *Int J Mol Sci* 2021; 22(3): 1001. https://doi.org/10.3390/ijms22031001.

129.Kaminski NE, Kaplan BLF. Immunomodulation by cannabinoids: Current uses, mechanisms, and identification of data gaps to be addressed for additional therapeutic application. *Adv Pharmacol* 2021; 91: 1-59. https://doi.org/10.1016/bs.apha.2021.01.001.

130.Espinosa-Riquer ZP, Ibarra-Sánchez A, Vibhushan S, Bratti M, Charles N, Blank U, et al. TLR4 receptor induces 2-AG-dependent tolerance to lipopolysaccharide and trafficking of CB2 receptor in mast cells. *J Immunol* 2019; 202(8): 2360-2371. https://doi.org/10.4049/jimmunol.1800997.

131.Haspula D, Clark MA. Cannabinoid receptors: An update on cell signaling, pathophysiological roles and therapeutic opportunities in neurological, cardiovascular, and inflammatory diseases. *Int J Mol Sci* 2020; 21(20): 7693. https://doi.org/10.3390/ijms21207693.

132.Kaur I, Behl T, Bungau S, Zengin G, Kumar A, El-Esawi MA, et al. The endocannabinoid signaling pathway as an emerging target in pharmacotherapy, earmarking mitigation of destructive events in rheumatoid arthritis. *Life Sci* 2020; 257: 118109. https://doi.org/10.1016/j.lfs.2020.118109.

133.Ferrini ME, Hong S, Stierle A, Stierle D, Stella N, Roberts K, et al. CB2 receptors regulate natural killer cells that limit allergic airway inflammation in a murine model of asthma. *Allergy* 2017; 72(6): 937-947. https://doi.org/10.1111/all.13107.

134.Levy JM. Endogenous cannabinoids may regulate chronic inflammation in aspirin-exacerbated respiratory disease. *World J Otorhinolaryngol*

Head Neck Surg 2020; 6(4): 255-257. https://doi.org/10.1016/j.wjorl.2020.07.004.

135. Christofides A, Konstantinidou E, Jani C, Boussiotis VA. The role of peroxisome proliferator-activated receptors (PPAR) in immune responses. *Metabolism* 2021; 114: 154338. https://doi.org/10.1016/j.metabol.2020.154338.

136. Boese AC, Lee JP, Hamblin MH. Neurovascular protection by peroxisome proliferator-activated receptor alpha in ischemic stroke. *Exp Neurol* 2020; 331: 113323. https://doi.org/10.1016/j.expneurol.2020.113323.

137. Zarei M, Aguilar-Recarte D, Palomer X, Vázquez-Carrera M. Revealing the role of peroxisome proliferator-activated receptor beta/delta in nonalcoholic fatty liver disease. *Metabolism* 2021; 114: 154342. https://doi.org/10.1016/j.metabol.2020.154342.

138. Skat-Rørdam J, Højland Ipsen D, Lykkesfeldt J, Tveden-Nyborg P. A role of peroxisome proliferator-activated receptor gamma in non-alcoholic fatty liver disease. *Basic Clin Pharmacol Toxicol* 2019; 124(5): 528-537. https://doi.org/10.1111/bcpt.13190.

139. Croasdell A, Duffney PF, Kim N, Lacy SH, Sime PJ, Phipps RP. PPAR γ and the innate immune system mediate the resolution of inflammation. *PPAR Res* 2015; 2015: 549691. https://doi.org/10.1155/2015/549691.

140. Magadum A, Engel FB. PPARβ/δ: Linking metabolism to regeneration. *Int J Mol Sci* 2018; 19(7): 2013. https://doi.org/10.3390/ijms19072013.

141. Korbecki J, Bobiński R, Dutka M. Self-regulation of the inflammatory response by peroxisome proliferator-activated receptors. *Inflamm Res* 2019; 68(6): 443-458. https://doi.org/10.1007/s00011-019-01231-1.

142. Vitale SG, Laganà AS, Nigro A, La Rosa VL, Rossetti P, Rapisarda AM, et al. Peroxisome proliferator-activated receptor modulation during metabolic diseases and cancers: Master and minions. *PPAR Res* 2016; 2016: 6517313. https://doi.org/10.1155/2016/6517313.

143. Lamichane S, Dahal Lamichane B, Kwon SM. Pivotal roles of peroxisome proliferator-activated receptors (PPARs) and their signal cascade for cellular and whole-body energy homeostasis. *Int J Mol Sci* 2018; 19(4): 949. https://doi.org/10.3390/ijms19040949.

144. Timmermans S, Souffriau J, Libert C. A general introduction to glucocorticoid biology. *Front Immunol* 2019; 10: 1545. https://doi.org/10.3389/fimmu.2019.01545.

145. Wepler M, Preuss JM, Merz T, Hartmann C, Wachter U, McCook O, et al. Impaired glucocorticoid receptor dimerization aggravates LPS-induced circulatory and pulmonary dysfunction. *Front Immunol* 2020; 10: 3152. https://doi.org/10.3389/fimmu.2019.03152.

146. Escoter-Torres L, Greulich F, Quagliarini F, Wierer M, Uhlenhaut NH. Anti-inflammatory functions of the glucocorticoid receptor require DNA binding. *Nucleic Acids Res* 2020; 48(15): 8393-8407. https://doi.org/10.1093/nar/gkaa565.

147. Liu X, Wang Y, Ortlund EA. First high-resolution crystal structures of the glucocorticoid receptor ligand-binding domain-peroxisome proliferator-activated gamma coactivator 1-alpha complex with endogenous and synthetic glucocorticoids. *Mol Pharmacol* 2019; 96(4): 408-417. https://doi.org/10.1124/mol.119.116806.

148. Ramos-Ramírez P, Tliba O. Glucocorticoid receptor beta (GRbeta): Beyond its dominant-negative function. *Int J Mol Sci* 2021; 22(7): 3649. https://doi.org/10.3390/ijms22073649.

149. Caramori G, Nucera F, Mumby S, Lo Bello F, Adcock IM. Corticosteroid resistance in asthma: Cellular and molecular mechanisms. *Mol Aspects Med* 2021; 85: 100969. https://doi.org/10.1016/j.mam.2021.100969.

150. Shimba A, Ikuta K. Control of immunity by glucocorticoids in health and disease. *Semin Immunopathol* 2020; 42(6): 669-680. https://doi.org/10.1007/s00281-020-00827-8.

151. Poma P. NF-kappaB and disease. *Int J Mol Sci* 2020; 21(23): 9181. https://doi.org/10.3390/ijms21239181.

152. Carrà G, Lingua MF, Maffeo B, Taulli R, Morotti A. P53 vs NF-kappaB: The role of nuclear factor-kappa B in the regulation of p53 activity and vice versa. *Cell Mol Life Sci* 2020; 77(22): 4449-4458. https://doi.org/10.1007/s00018-020-03524-9.

153. Rasmi RR, Sakthivel KM, Guruvayoorappan C. NF-kappaB inhibitors in treatment and prevention of lung cancer. *Biomed Pharmacother* 2020; 130: 110569. https://doi.org/10.1016/j.biopha.2020.110569.

154. Zhao J, Xie F, Chen R, Zhang Z, Dai R, Zhao N, et al. Transcription factor NF-kappaB promotes acute lung injury via microRNA-99b-mediated PRDM1 down-regulation. *J Biol Chem* 2020; 295(52): 18638-18648. https://doi.org/10.1074/jbc.RA120.014861.

155. Zakeri A, Russo M. Dual Role of toll-like receptors in human and experimental asthma models. *Front Immunol* 2018; 9: 1027. https://doi.org/10.3389/fimmu.2018.01027.

156. Chang M, Zhang Y, Hui Z, Wang D, Guo H. IFRD1 regulates the asthmatic responses of airway via NF-kappaB pathway. *Mol Immunol* 2020; 127: 186-192. https://doi.org/10.1016/j.molimm.2020.09.010.

157. Dai R, Niu M, Wang N, Wang Y. Syringin alleviates ovalbumin-induced lung inflammation in BALB/c mice asthma model via NF-kappaB signaling pathway. *Environ Toxicol* 2021; 36(3): 433-444. https://doi.org/10.1002/tox.23049.

158. Kim E, Ahuja A, Kim MY, Cho JY. DNA or protein methylation-dependent regulation of activator protein-1 function. *Cells* 2021; 10(2): 461. https://doi.org/10.3390/cells10020461.

159. Birnhuber A, Biasin V, Schnoegl D, Marsh LM, Kwapiszewska G. Transcription factor Fra-2 and its emerging role in matrix deposition, proliferation and inflammation in chronic lung diseases. *Cell Signal* 2019; 64: 109408. https://doi.org/10.1016/j.cellsig.2019.109408.

160. Henderson I, Caiazzo E, McSharry C, Guzik TJ, Maffia P. Why do some asthma patients respond poorly to glucocorticoid therapy? *Pharmacol Res* 2020; 160: 105189. https://doi.org/10.1016/j.phrs.2020.105189.

161. Palumbo ML, Prochnik A, Wald MR, Genaro AM. Chronic stress and glucocorticoid receptor resistance in asthma. *Clin Ther* 2020; 42(6): 993-1006. https://doi.org/10.1016/j.clinthera.2020.03.002.

162. Vettorazzi S, Bode C, Dejager L, Frappart L, Shelest E, Klaßen C, et al. Glucocorticoids limit acute lung inflammation in concert with inflammatory stimuli by induction of SphK1. *Nat Commun* 2015; 6: 7796. https://doi.org/10.1038/ncomms8796.

163. Agrawal S, He JC, Tharaux PL. Nuclear receptors in podocyte biology and glomerular disease. *Nat Rev Nephrol* 2021; 17(3): 185-204. https://doi.org/10.1038/s41581-020-00339-6.

164. Van Moortel L, Gevaert K, De Bosscher K. Improved glucocorticoid receptor ligands: Fantastic beasts, but how to find them? *Front Endocrinol (Lausanne)* 2020; 11: 559673. https://doi.org/10.3389/fendo.2020.559673.

165. Rogliani P, Ritondo BL, Puxeddu E, Pane G, Cazzola M, Calzetta L. Experimental glucocorticoid receptor agonists for the treatment of asthma: A systematic review. *J Exp Pharmacol* 2020; 12: 233-254. https://doi.org/10.2147/JEP.S237480.

166. Muralikumar S, Vetrivel U, Narayanasamy A, Das UN. Probing the intermolecular interactions of PPARγ-LBD with polyunsaturated fatty acids and their anti-inflammatory metabolites to infer most potential binding moieties. *Lipids Health Dis* 2017; 16(1): 17. https://doi.org/10.1186/s12944-016-0404-3.

167. Monga N, Sethi GS, Kondepudi KK, Naura AS. Lipid mediators and asthma: Scope of therapeutics. *Biochem Pharmacol* 2020; 179: 113925. https://doi.org/10.1016/j.bcp.2020.113925.

168. Arita M. Eosinophil polyunsaturated fatty acid metabolism and its potential control of inflammation and allergy. *Allergol Int* 2016; 65 Suppl: S2-S5. https://doi.org/10.1016/j.alit.2016.05.010.

169. Stoodley I, Garg M, Scott H, Macdonald-Wicks L, Berthon B, Wood L. Higher omega-3 index is associated with better asthma control and lower medication dose: A cross-sectional study. *Nutrients* 2019; 12(1): 74. https://doi.org/10.3390/nu12010074.

170. Mochimaru T, Fukunaga K, Miyata J, Matsusaka M, Masaki K, Kabata H, et al. 12-OH-17,18-epoxyeicosatetraenoic acid alleviates eosinophilic

airway inflammation in murine lungs. *Allergy* 2018; 73(2): 369-378. https://doi.org/10.1111/all.13297.

171. Allaire J, Harris WS, Vors C, Charest A, Marin J, Jackson KH, et al. Supplementation with high-dose docosahexaenoic acid increases the Omega-3 Index more than high-dose eicosapentaenoic acid. *Prostaglandins Leukot Essent Fatty Acids* 2017; 120: 8-14. https://doi.org/10.1016/j.plefa.2017.03.008.

172. Fussbroich D, Colas RA, Eickmeier O, Trischler J, Jerkic SP, Zimmermann K, et al. A combination of LCPUFA ameliorates airway inflammation in asthmatic mice by promoting pro-resolving effects and reducing adverse effects of EPA. *Mucosal Immunol* 2020; 13(3): 481-492. https://doi.org/10.1038/s41385-019-0245-2.

173. Nagel G., Linseisen J. Dietary intake of fatty acids, antioxidants and selected food groups and asthma in adults. *Eur J Clin Nutr* 2005; 59(1): 8-15. https://doi.org/10.1038/sj.ejcn.1602025.

174. Dreßler M, Fussbroich D, Böhler L, Herrmann E, Benker N, Tytyk M, et al. Oil supplementation with a special combination of n-3 and n-6 long-chain polyunsaturated fatty acids does not protect for exercise induced asthma: A double-blind placebo-controlled trial. *Lipids Health Dis* 2020; 19(1): 167. https://doi.org/10.1186/s12944-020-01343-2.

175. Yeates AJ, Zavez A, Thurston SW, McSorley EM, Mulhern MS, Alhamdow A, et al. Maternal long-chain polyunsaturated fatty acid status, methylmercury exposure, and birth outcomes in a high-fish-eating mother-child cohort. *J Nutr* 2020; 150(7): 1749-1756. https://doi.org/10.1093/jn/nxaa131.

176. Elshani B, Kotori V, Daci A. Role of omega-3 polyunsaturated fatty acids in gestational diabetes, maternal and fetal insights: Current use and future directions. *J Matern Fetal Neonatal Med* 2021; 34(1): 124-136. https://doi.org/10.1080/14767058.2019.1593361.

177. Miyata J, Arita M. Role of omega-3 fatty acids and their metabolites in asthma and allergic diseases. *Allergol. Int* 2015; 64(1): 27-34. https://doi.org/10.1016/j.alit.2014.08.003.

178. Yang ZH, Amar M, Sampson M, Courville AB, Sorokin AV, Gordon SM, et al. Comparison of omega-3 eicosapentaenoic acid versus docosahexaenoic acid-rich fish oil supplementation on plasma lipids and lipoproteins in normolipidemic adults. *Nutrients* 2020; 12(3): 749. https://doi.org/10.3390/nu12030749.

179. Wang Y, Tu R, Yuan H, Shen L, Hou J, Liu X, et al. Associations of unhealthy lifestyles with metabolic syndrome in Chinese rural aged females. *Sci Rep* 2020; 10(1): 2718. https://doi.org/10.1038/s41598-020-59607-x.

180. Piazzi G, D'Argenio G, Prossomariti A, Lembo V, Mazzone G, Candela M, et al. Eicosapentaenoic acid free fatty acid prevents and suppresses colonic neoplasia in colitis-associated colorectal cancer acting on Notch signaling and gut microbiota. *Int J Cancer* 2014; 135(9): 2004-2013. https://doi.org/10.1002/ijc.28853.

181. Williams NC, Hunter KA, Shaw DE, Jackson KG, Sharpe GR, Johnson MA. Comparable reductions in hyperpnoea-induced bronchoconstriction and markers of airway inflammation after supplementation with 6·2 and 3·1 g/d of long-chain n-3 PUFA in adults with asthma. *Br J Nutr* 2017; 117(10): 1379-1389. https://doi.org/10.1017/S0007114517001246.

Authors:

Oxana Yu. Kytikova – MD, DSc, Senior Researcher, Laboratory of Rehabilitative Treatment, Vladivostok Branch of Far Eastern Scientific Center for Physiology and Pathology of Respiration, Scientific Research Institute of Medical Climatology and Rehabilitation Therapy, Vladivostok, Russia. http://orcid.org/0000-0001-5018-0271.

Yulia K. Denisenko – DSc, Head of the Laboratory of Biomedical Research, Vladivostok Branch of Far Eastern Scientific Center for Physiology and Pathology of Respiration, Scientific Research Institute of Medical Climatology and Rehabilitation Therapy, Vladivostok, Russia. https://orcid.org/0000-0003-4130-8899.

Tatyana P. Novgorodtseva – DSc, Professor, Principal Researcher, Laboratory of Biomedical Research, Vladivostok Branch of Far Eastern Scientific Center for Physiology and Pathology of Respiration, Scientific Research Institute of Medical Climatology and Rehabilitation Therapy, Vladivostok, Russia. http://orcid.org/0000-0002-6058-201X.

Ivan S. Kovalenko – PhD student, Laboratory of Biomedical Research, Vladivostok Branch of Far Eastern Scientific Center for Physiology and Pathology of Respiration, Scientific Research Institute of Medical Climatology and Rehabilitation Therapy, Vladivostok, Russia. http://orcid.org/0000-0002-7404-7501.

Marina V. Antonyuk – MD, DSc, Professor, Head of the Laboratory of Rehabilitative Treatment, Vladivostok Branch of Far Eastern Scientific Center for Physiology and Pathology of Respiration, Scientific Research Institute of Medical Climatology and Rehabilitation Therapy, Vladivostok, Russia. https://orcid.org/0000-0002-2492-3198.