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The Role of the Lysophosphatide Acid in the Pathogenesis of Bronchial Asthma

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Abstract. Lysophospholipids are bioactive lipid mediators localized in cell membranes. They influence cell proliferation, differentiation, survival, migration, adhesion, invasion and morphogenesis, and are also associated with neurogenesis, angiogenesis, fibrogenesis and tumorigenesis.

Key words: nuclear receptors, peroxisome proliferator-activated receptors.

In recent years, the signaling function of lysophospholipids, in particular lysophosphatidic acid (LPA, lysophosphatidic acid), has been actively studied in various diseases and pathological conditions. At the same time, not much attention has been paid to studying the role of LPA in the pathogenesis of bronchopulmonary diseases, in particular bronchial asthma (BA). It is known that LPA interacts with LPA receptors 1–6 (LPARs, lysophosphatidic acid receptors), nuclear receptors, peroxisome proliferator-activated receptors (PPARs, peroxisome proliferator-activated receptors), actin binding proteins (ABP, actin binding proteins) and, as recently discovered, with transient receptor potential (TRP) ion channel receptors, which results in the activation of multiple signaling pathways. The role of LPA receptors in the pathogenesis of asthmatic reactions is being actively studied, but in recent years. Over the years, the focus of research has noticeably shifted to the interaction of LPA with TRP channel receptors. With the establishment of the mechanism of interaction of LPA with LPARs and TRP receptors in the bronchopulmonary system, a new perspective is opened not only on understanding the mechanisms of initiation of asthmatic reactions, but also on possible ways to control them. This suggests fundamentally new opportunities in the development of an effective therapeutic strategy for asthma at the stage of correction of the development of asthmatic reactions. Manipulating LPA signaling through targeting LPAR1–6 is a current pharmacological target. However, LPA signaling through its receptors is also associated with stimulation of development

fibrosis, triggering the processes of atherogenesis, oncogenesis and metastasis. Thus, the use of LPA agonists faces the dilemma of using the therapeutically effective mechanisms of action of this lipid molecule while avoiding the development of undesirable effects, which makes it relevant to study other LPA receptors as therapeutic targets. This article summarizes the latest literature data on the chemical structure, biosynthetic pathways and receptors of LPA. The main attention is paid to the role of LPA, LPARs and TRP channels in the pathogenesis of AD. Possible therapeutic strategies for AD targeting LPA, LPARs and TRP channels are summarized and discussed. The review included sources of information that addressed issues relevant to the purpose of this review.

LYSOPHOSPHATIDE ACID.

Lysophosphatidic acid belongs to the class of lysoglycerophospholipids - phospholipids with only one

fatty acid residue, in contrast to glycerophospholipids, which have two fatty acids (FA) in the sn-1 and sn-2 positions.

Lysophosphatidic acids are represented by different molecular species depending on the presence of saturated or unsaturated fatty acid residues in their structure (LPA16:0, LPA18:0, LPA18:1, LPA18:2, LPA20:4 and LPA22:6). Also, the structure and activity of LPA are determined by the position of fatty acids in the glycerol molecule. LPA biosynthesis occurs through several pathways.

In the first pathway, LPA biosynthesis depends on the activity of phospholipases. This pathway involves the breakdown of membrane phospholipids (phosphatidylcholine, phosphatidylserine and phosphatidylethanolamine) or the breakdown of diacylglycerol (DAG, diacyl glycerol) to form phosphatidic acid. Phosphatidic acid

is a substrate for phospholipases A1 and A2, which release FAs from the sn-1 or sn-2 positions, respectively, forming LPA. Phospholipase A1 acts both extracellularly and intracellularly. Extracellular phospholipase A1 is involved in triacylglycerol hydrolysis and fatty acid breakdown. Phospholipase A2 is a large superfamily comprising 15 groups and 30 isoforms belonging to four types: secretory (IB, IIA, IIC, IID, IIE, IIF, III, V, X, XIIA and XIIB), cytosolic, calcium-independent and lipoprotein associated phospholipase A2. Phospholipase A2 hydrolyzes unsaturated fatty acids and is involved in the production of eicosanoids and platelet activating factor. On the one hand, secretory phospholipase A2 releases omega-3-polyunsaturated fatty acids, which are a substrate for anti-inflammatory and pro-resolving oxylipins, on the other hand, with the participation of secretory phospholipase A2, fatty acids, lysophosphatidic acid, lysophospholipids, prostaglandins, leukotrienes and thromboxanes are formed, which have pro-inflammatory effect.

In the second pathway, LPA biosynthesis occurs with the participation of autotaxin (ATC, autotaxin). Autotaxin (isoforms ATX-α, ATX-β, ATX-γ, ATX-δ and ATX-ε) or lysophospholipase D belongs to the class of extranuclear pyrophosphatases/phosphodiesterases (ENPP2, ectonucleotide pyrophosphatase/phosphodiesterase 2). Transcription of the ENPP2 gene, located in the 8q24 region of the human chromosome, is regulated by several proinflammatory and transcription factors. Inhibition of ATX leads to a decrease in the level of pro-inflammatory mediators (tumor necrosis factor, interleukin (IL) 1, IL-6) in the experiment. ATX is active in most body fluids, including serum/plasma, bronchoalveolar lavage fluid, cerebrospinal fluid, and urine.

In platelets, autotaxin can bind to platelet integrins αVβ3 and αIIbβ3. It is believed that the main source of autotaxin in the blood is adipose tissue. LPA is also formed from glycerol 3-phosphate via glycerol 3-phosphate acyltransferase. Finally, LPA can be cleaved to monoacylglycerol and diacylglycerol by lysophosphatases, to PA by LPA acyltransferase, and to G3P by lysophospholipases.

Lysophosphatidic acid receptors.

The physiological role of circulating LPA is to predominantly transmit signals through interaction with G-protein coupled transmembrane receptors (GPCRs, G-protein coupled receptors), which include LPA receptors (LPAR1–6). Additionally, recent studies have shown that LPA is a ligand for several TRP channels. LPAR1–3 belong to the endothelial differentiation gene (EDG) family: LPAR1/EDG2, LPAR2/EDG4 and LPAR3/EDG7. LPAR4 (P2RY9, GPR23), LPAR5 (GPR92) and LPAR6 (P2RY5, GPR87) belong to the group of purinergic receptors (P2Y, purinergic receptors). Recent studies have shown that LPA can also activate P2Y1. LPAR1 is widely expressed in various organs and tissues, but is more abundant in the brain, heart, placenta, colon and small intestine. Higher expression of LPAR2 mRNA was found in the kidneys, uterus, and testes, while lower expression was found in the thymus, pancreas, and spleen. LPAR3 mRNA levels are higher in the heart, lungs, pancreas, brain, prostate and ovaries. LPAR4 mRNA levels are increased in the skin, heart, ovaries, and thymus of mice. Large amounts of LPAR5 are expressed in the spleen, small intestine, and colon. LPAR6 has been implicated in hair growth, but studies of its role and mechanisms in various systems are relatively sparse. LPARs activate Gα protein subtypes (Gα12/13, Gαq/11, Gαi/o and Gαs) that modulate downstream signaling pathways. Thus, the ROCK (Rho/Rho-associated protein kinase) signaling pathway is activated through Gα12/13; Gαq/11 activates phospholipase C (PLC, phospholipase C) and then, through downstream cascades, GSK3 (glycogen synthase kinase 3) and CREB; Gαi/0 activates the PLC-CREB and GSK3 pathways, and also stimulates extracellular signal-regulated kinases 1/2 (ERK1/2), Akt/phosphoinositide 3-kinase (PI3K, PI3-kinase) and inhibits the production of cyclic adenosine monophosphate (cAMP) ; GαS modulates the activity of adenylate cyclase and protein kinase A (PKA, protein kinase A), activating the cAMP signaling pathway. Central to the effects of LPA is its ability to modulate the actin cytoskeleton through activation of the small GTPases Ras through Gαi/o (stimulation of extracellular Erk1/2 signals) and Rho through Gα12/13 (stimulation of ROCK). These receptors transmit a signal through MAPK, PLC and tyrosine kinases and initiate the synthesis of a number of transcription factors that interact with DNA regions and initiate proliferation, cell migration or intercellular interactions. LPA mediates multiple functions through LPARs, including Ca2+ mobilization, survival, proliferation, adhesion, cell migration, immune function, by reducing chemokine production and inhibiting cell migration, myelination.

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