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Review Article

Lysophospholipid receptors in drug discovery

Yasuyuki Kihara[a], *Hirotaka Mizuno*[a,b], *Jerold Chun*[a,*]

[a]*Department of Molecular and Cellular Neuroscience, Dorris Neuroscience Center, The Scripps Research Institute, DNC-118, 10550 N, Torrey Pines Road, La Jolla, CA 92037, USA*

[b]*Exploratory Research Laboratories, Ono Pharmaceutical Co., Ltd., Ibaraki 300-4247, Japan*

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ABSTRACT

Lysophospholipids (LPs), including lysophosphatidic acid (LPA), sphingosine 1-phospate (S1P), lysophosphatidylinositol (LPI), and lysophosphatidylserine (LysoPS), are bioactive lipids that transduce signals through their specific cell-surface G protein-coupled receptors, LPA_{1-6}, $S1P_{1-5}$, LPI_1, and $LysoPS_{1-3}$, respectively. These LPs and their receptors have been implicated in both physiological and pathophysiological processes such as autoimmune diseases, neurodegenerative diseases, fibrosis, pain, cancer, inflammation, metabolic syndrome, bone formation, fertility, organismal development, and other effects on most organ systems. Advances in the LP receptor field have enabled the development of novel small molecules targeting LP receptors for several diseases. Most notably, fingolimod (FTY720, Gilenya, Novartis), an S1P receptor modulator, became the first FDA-approved medicine as an orally bioavailable drug for treating relapsing forms of multiple sclerosis. This success is currently being followed by multiple, mechanistically related compounds targeting S1P receptor subtypes, which are in various stages of clinical development. In addition, an LPA_1 antagonist, BMS-986020 (Bristol-Myers Squibb), is in Phase 2 clinical development for treating idiopathic pulmonary fibrosis, as a distinct compound, SAR100842 (Sanofi) for the treatment of systemic sclerosis and related fibrotic diseases. This review summarizes the current state of drug discovery in the LP receptor field.

Contents

Abbreviations: LP, Lysophospholipid; LPA, lysophosphatidic acid; S1P, sphingosine 1-phospate; LPI, lysophosphatidylinositol; LysoPS, lysophosphatidylserine; LPC, lysophosphatidylcholine; LPE, lysophosphatidylethanolamine; LPG, lysophosphatidylglycerol; ATX, autotaxin; Sphk, sphingosine kinases; GPCR, G protein-coupled receptor; MS, multiple sclerosis; EAE, experimental autoimmune encephalomyelitis; NMO, neuromyelitis optica; IPF, idiopathic pulmonary fibrosis; FDA, Food and Drug Administration; EMA, European Medicines Agency; NLM ID, National Laboratory of Medicine Identifier.

*Corresponding author.
E-mail address: jchun@scripps.edu (J. Chun).

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Introduction

Lysophospholipids (LPs) such as lysophosphatidic acid (LPA) and sphingosine 1-phosphate (S1P) are a class of bioactive lipids [1,2], which have a phosphate head group and a single fatty acyl chain attached to a 3-carbon backbone in their chemical structures. LPs have a fairly long history dating back to the early 20th century, but the field has shown markedly accelerated growth in recent decades (Fig. 1A). LPA and S1P are the best studied LPs and play pivotal roles in physiological events including cell proliferation, survival, motility, cytoskeletal changes, and electrophysiological changes as well as pathophysiological processes that include autoimmune disease, fibrotic disease, cancer, inflammation, bone diseases, pain, metabolic syndrome, infertility, and hair loss. LPA is produced through several enzymatic pathways. Lysophospholipase D (known as autotaxin, ATX) liberates a choline group from lysophosphatidylcholine (LPC), whereas phospholipase A_1 and A_2 deacylate phosphatidic acid to produce 2-acyl and 1-acyl LPA, respectively [2]. Importantly, LPA is also *de novo* synthesized from glycerol-3-phosphate by the action of acyltransferases [3]. By comparison, S1P is produced by phosphorylation of sphingosine *via* the sphingosine kinases, Sphk1/2 [4].

LPs exert their effects by binding to specific G protein-coupled receptors (GPCRs) [5] that are the largest membrane receptor family in the human genome and contain nearly 800 receptors (including olfactory receptors) [6]. There are currently six LPA (LPA_{1-6}) and five S1P receptors ($S1P_{1-5}$) [2,7,8]. Recently, lysophosphatidylinositol (LPI) and lysophosphatidylserine (LysoPS) have been also shown to activate cognate GPCRs [9]. About 40 receptors within the 350 non-olfactory GPCRs have been identified as lipid GPCRs to date, of which ~40% are LP receptors (Fig. 1B). It is likely that additional receptors for LPLs may

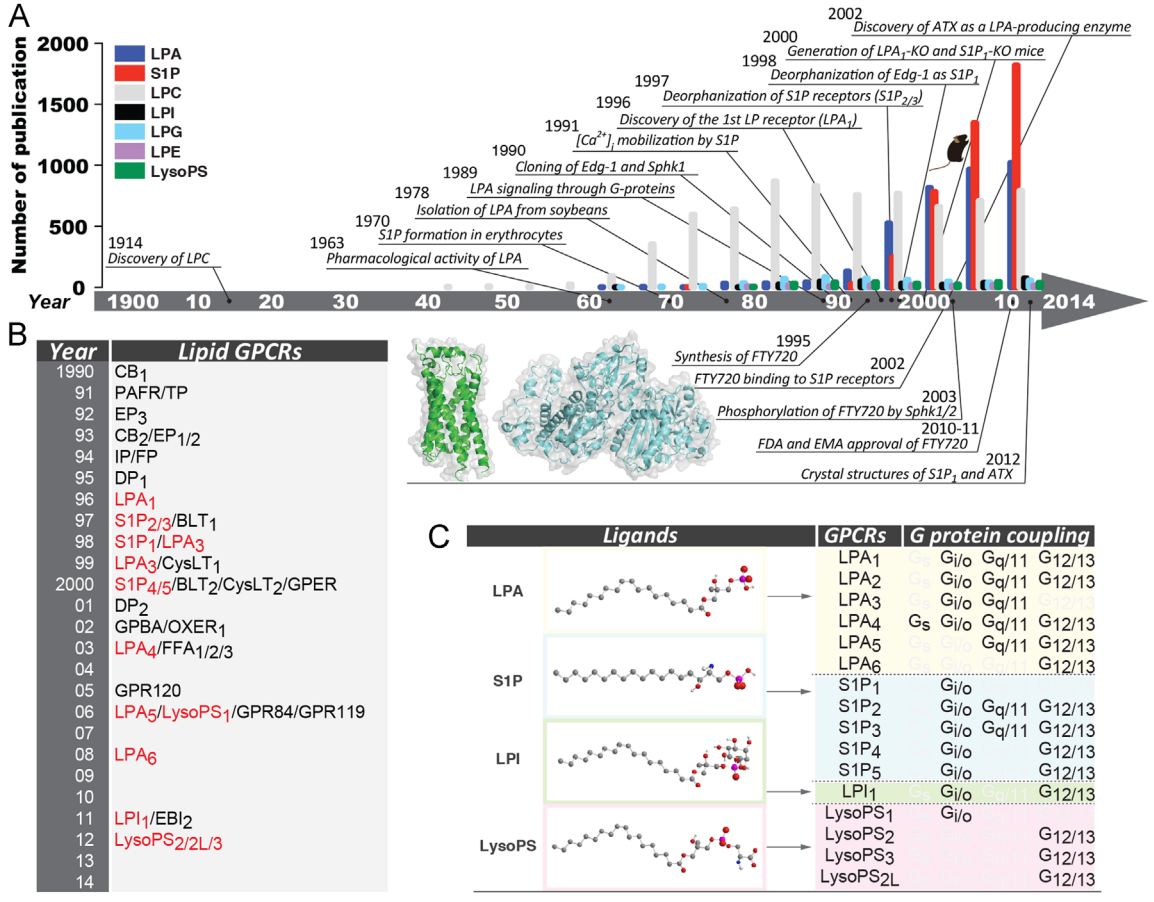

Fig. 1 – Chronology of the LP field, LP and other lipid receptors, and overview of proximal LP signaling features. (A) Chronology of the LP receptor field. Vertical bars indicate the number of publications within 5-year bins, which were searched in PubMed with unabbreviated names of the indicated keywords. (B) Chronological table for identification of lipid GPCRs. LP receptors are noted in red. (C) The chemical structures of LPs, GPCR names, and associated heterotrimeric G-proteins as defined by their Gα subunits.

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