BPB Reports

*Review*

# Inositolphospholipids and GPR55

Akira Ito, Jumpei Omi, and Junken Aoki*

*Department of Health Chemistry, Graduate School of Pharmaceutical Sciences, The University of Tokyo, 7-3-1, Hongo, Bunkyo-ku, Tokyo, Japan*
Received April 16, 2024; Accepted April 24, 2024

**Phospholipids, the major components of biological membranes, usually have two fatty acids. Less common are the lysophospholipids, which have only one fatty acid. Like prostaglandins and leukotrienes, some lysophospholipids serve as mediators to regulate various cellular functions through G protein-coupled receptors (GPCRs). This review focuses on a lysophospholipid with an inositol head, lysophosphatidylinositol (LPI), and summarizes its distribution, alterations, metabolic mechanisms, and physiological and pathological functions. In addition, we will summarize the current knowledge of GPR55, a proposed G protein-coupled receptor for LPI, with a particular focus on its functions in cancer and immune responses.**

**Key words** lysophosphatidylinositol, phosphatidylinositol, GPR55, lysophospholipid, G protein-coupled receptor, lipid mediator

## INTRODUCTION: DIACYLPHOSPHOLIPIDS AND LYSOPHOSPHOLIPIDS

Glycerophospholipids (more simply phospholipids or PLs) are the major components of biomembranes and are mainly classified according to their polar heads. The major PLs include phosphatidylcholine (PC), sphingomyelin (SM), and phosphatidylethanolamine (PE), while minor PLs include phosphatidylglycerol (PG), phosphatidylinositol (PI), phosphatidylserine (PS), and phosphatidic acid (PA). In addition to the differences in the polar head, there are also various PL molecular species that differ in their fatty acid moieties. These diverse PLs are distributed in different proportions on the two sides of the PL bilayers, *i.e.*, extracellular and intracellular sides, depending on the polar head and fatty acid moiety, and exert various biological functions by forming special membrane domains within the PL bilayer and influencing the function of specific membrane proteins.

Most PLs in living organisms are diacyl PLs with two fatty acids, while lysophospholipids (LPLs), which are two to three orders of magnitude less common, have only one fatty acid. Phospholipase As (PLAs) are enzymes that hydrolyze the fatty acid esters of diacyl PLs to produce LPLs. They are classified into two groups based on differences in the position of the fatty acids hydrolyzed. Phospholipase $A_1$s ($PLA_1$s) act on a fatty acid at the *sn*-1 position, while phospholipase $A_2$s ($PLA_2$s) act on at the *sn*-2 position (Fig. 1). More than 50 different $PLA_2$s and about 10 $PLA_1$s have been described so far in mammals.[1,2] When acting on PLs, PLAs produce one LPL and one fatty acid, but which product is needed depends on the situation. For example, the best characterized cytoplasmic $PLA_2$ ($cPLA_2$/PLA2G4) selectively releases arachidonic acid from PLs and is involved in the production of eicosanoids such as prostaglandins and leukotrienes.[1] By contrast, phosphatidic acid-selective $PLA_1$ (PA-$PLA_1\alpha$) is expressed in specific cells in hair follicles and selectively hydrolyzes fatty acids at the

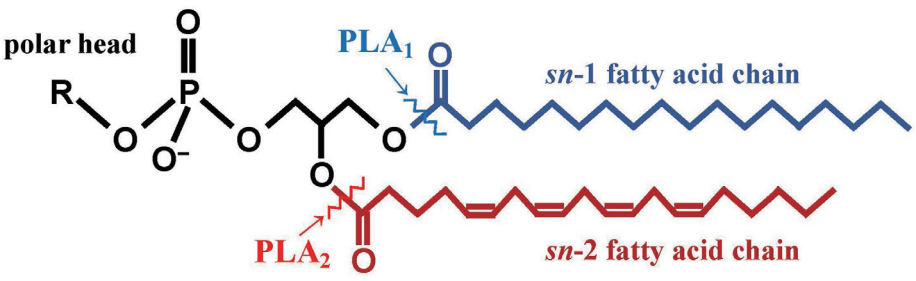


**Fig. 1.** Structure of Glycerophospholipids and the Position Phospholipase $A_1$ and Phospholipase $A_2$ Cleave

Glycerophospholipids consist of two hydrophobic fatty acid chains at the *sn*-1 and *sn*-2 positions and a hydrophilic polar head at the *sn*-3 position attached to the glycerol backbone via two ester bonds and one phosphodiester bond, respectively. The polar head groups (R) include choline, serine, ethanolamine, glycerol, inositol, and glucose, etc. Relatively weak ester bonds in the fatty acid chain can be cleaved by phospholipase $A_1$ or phospholipase $A_2$ to generate a lysophospholipid and a fatty acid.

*To whom correspondence should be addressed. e-mail: jaoki@mol.f.u-tokyo.ac.jp

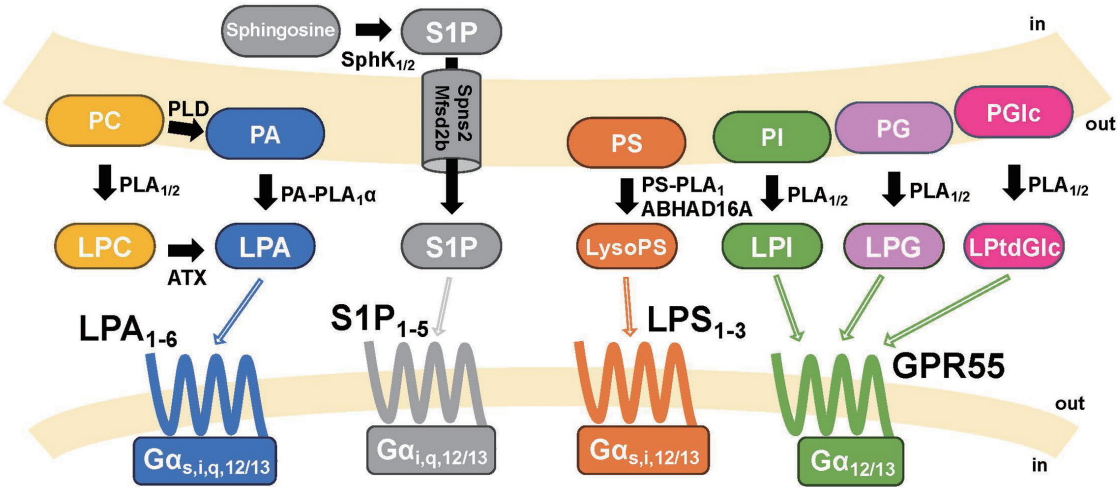


**Fig. 2.** Pathways of Lysophospholipid (LPL) Production and Their Receptors

This schematic diagram shows the pathways by which lysophospholipids (LPLs) are produced from diacylphospholipids in biological membranes, together with the enzymes related to phospholipid metabolism. All LPL receptors are classified as seven-transmembrane GPCRs and are known to be involved in various cellular functions via several different types of Gα proteins. There are six GPCRs for LPA, five for S1P, 3 for LysoPS (in the case of human) and one for LPI. GPR55 can be activated by various lysophospholipids other than LPI, such as LPG and LPtdGlc.

*sn*-1 position of PA in the outer membrane to produce lysophosphatidic acid (LPA), which then activates the LPA-specific LPA receptor $LPA_6$ on adjacent hair follicle cells, thereby contributing to the formation of the correct layer structure of the hair follicles.[2,3,4] Thus, lysophospholipids not only function as bioactive molecules by themselves,[5] but are also degradation products of PL metabolism. Besides, in the PL fatty acid remodeling reaction (also known as Land's cycle), LPLs are important intermediates. Unlike other LPLs, LPA also serves as an intermediate metabolite in the *de novo* PL synthetic pathway. As stated above, LPLs have a variety of roles. Here, we focus on the functions of LPLs mediated by G protein-coupled receptors (GPCRs) (LPL mediators), especially lysophosphatidylinositol (LPI), which has a sugar inositol moiety at its polar head, with comparison to other LPL mediators (Fig. 2).

## LYSOPHOSPHATIDYLINOSITOL (LPI)

LPI is thought to result from deacylation of phosphatidylinositol (PI) by the action of $PLA_1$ or $PLA_2$. PI is a major component of cellular PLs in higher organisms including mammals, and LPI is therefore thought to be present in almost all cells, albeit in varying amounts. In fact, when LPLs in various cells and tissues were analyzed using a highly sensitive LPL detection system developed by the authors, LPI was detected in all cells and tissues tested (our in-house data).

***In Vivo* Presence** Like other LPLs, LPI is widely present *in vivo*. Table 1 shows the concentrations of various LPLs in human plasma. The most abundant LPL in the plasma is lysophosphatidylcholine (LPC), with concentrations reaching several hundred μM. LPC is constantly produced from PC on lipoproteins by the action of lecithin-cholesterol acyltransferase (LCAT) and lipases (mainly lipoprotein, hepatic and endothelial lipases).[6] On the other hand, the concentration of LPA and lysophosphatidylserine (LysoPS), which are known to function as bioactive LPLs via specific GPCRs, are much lower than the concentration of LPC, ranging from a few to several dozen nM. The plasma concentration of LPI, the main LPL discussed in this review, is relatively high at several μM. Plasma contains about 50 μM phosphatidylinositol (PI), and LPI in plasma is thought to be generated by deacylation of PI by PLAs.

**Table 1.** Concentration of Lysophospholipids in Human Plasma Under Normal Conditions

| Lysophospholipids | Concentration in Plasma |
|---|---|
| Lysophosphatidylcholine (LPC) | 100~300 μM |
| Lysophosphatidylethanolamine (LPE) | ~10 μM |
| Lysophosphatidylinositol (LPI) | 1~10 μM |
| Lysophosphatidylglycerol (LPG) | 100~500 nM |
| Lysophosphatidic acid (LPA) | ~50 nM |
| Lysophosphatidylserine (LysoPS) | Not detected (< 10 nM) |
| Sphingosine monophosphate (S1P) | 1~5 μM |

The sources of LPI and PI detected in the plasma are not known. However, it is reasonable to assume that most of the plasma PLs including PI an LPI originate from the liver. This is because 1) the fatty acid composition of PC in the plasma is similar to that of PC in liver, 2) most of the plasma PLs are present on lipoproteins,[7] and 3) lipoproteins are produced and secreted by the liver.

LPI is also present in a variety of cultured cells and tissues and may be derived from deacylation of PI. It is not clear how LPI is produced in these cells and tissues, one report indicated that a cytoplasmic $PLA_1$, called DDHD1 or PA-$PLA_1$, is involved in the production of LPI.[8]

**LPI and Cell Proliferation** LPI abundance is reported to change at the cell and animal levels. Alonso *et al.*[9] analyzed PLs in the cells transformed with Ras and found that oncogenic transformation enhanced inositol PL metabolism, resulting in increased PI and LPI levels. Furthermore, Corda's group indicated the involvement of PI-specific $PLA_2$ in the produc-

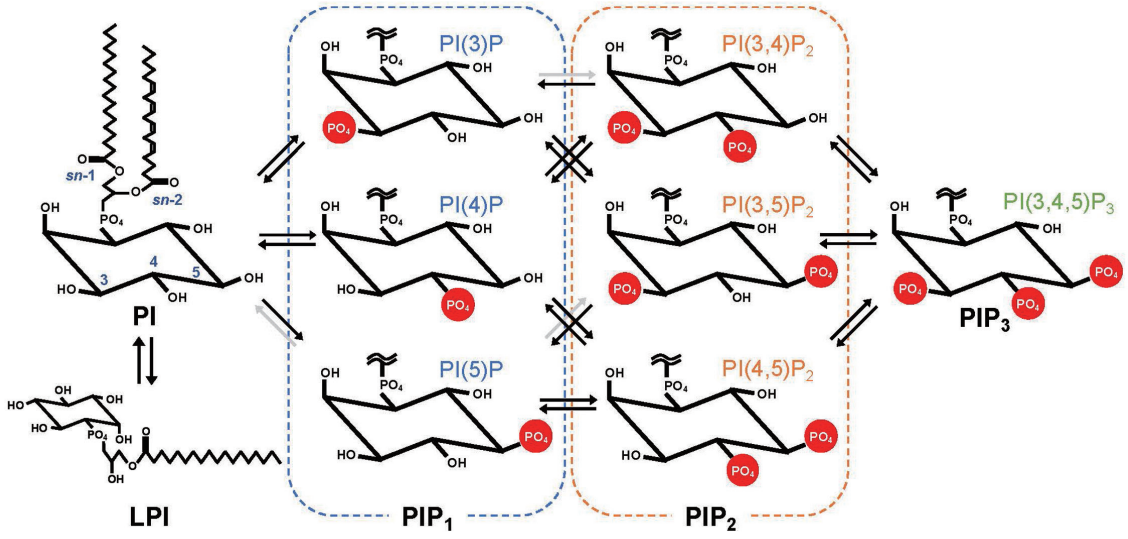


**Fig. 3.** Structures of PI, LPI and PIPs

Chemical structures of PI, LPI and PIPs are shown. Note that the fatty acid chains are omitted for PIPs. LPI is formed by hydrolysis of the fatty acid at the *sn*-1 or *sn*-2 position of PI by phospholipase As (PLAs). LPI can be acylated by lysophosphatidylinositol acyltransferase 1 (LPIAT1) to be PI. PIPs are produced by the stepwise addition and/or removal of phosphate groups at the 3′, 4′ and 5′ hydroxy groups of PI. Rightward reactions are carried out by phosphoinositide kinases and the leftward by phosphatases.

tion of LPI by Ras transformation.[10] They also suggested that LPI enhances cell proliferation, and thus they proposed that LPI is a bioactive lipid with a cell proliferation stimulation activity.

**LPI and Cancer** Increased levels of LPI have been observed in several types of human cancer cell lines, including ovarian, lung and thyroid cancer cells.[11,12,13] These studies pointed to the usefulness of blood phospholipids as cancer biomarkers. LPI levels are higher in human colorectal cancer tissues than in normal tissues.[14,15] Similar cancerous changes in LPI have been also reported in Ulcerative colitis (UC)-related colorectal cancer.[16]

**PI and PIPs and Cancer** PI is also converted to phosphatidyl inositol phosphates (PIPs) as well as LPI. (Fig. 3). The levels of PI and their fatty acid compositions have been found to change in some cancer tissues. For example, Kawashima *et al.* showed that PI containing arachidonic acid (20:4) was the major PI species in normal tissues, while in breast cancer tissues, 20:4-PI was greatly reduced and the proportion of PI molecular species with fatty acids such as 18:1 and 20:3 was increased.[17,18] These changes in PI molecular species were particularly pronounced in the superficial layers of cancer tissues, suggesting a relationship with the invasive potential of cancer cells.

Deletion of the tumor suppressor gene PTEN, a PIP3 phosphatase, has been observed in many cancers, and variation in PIPs levels has also been observed in many cancer types, with increases in PIP1 and decreases in PIP2 and PIP3. A decrease in the number of double bonds in the fatty acid portion of PI and PIPs is remarkable.[19] It is likely that changes in the saturation of fatty acid chains in PI and PIPs affect the behavior of cancer cells. For example, analysis of human colorectal cancer-derived spheroids revealed that arachidonic acid-containing PI (18:0/20:4) accumulated at the outer edge of tumor tissue, suggesting that arachidonic acid-containing PI has some roles in the migratory and invasive properties of cancer cells.[20] These reports suggest that PI is actively metabolized in tumors, creating an environment in which LPI is readily produced.

## BIOLOGICAL ACTIONS OF LPI

**LPI Receptors** As stated above, LPI has been considered to be a bioactive lipid involved in cell proliferation because LPI level is high in cells with active cell proliferation *in vitro* and also in cancer tissues. The LPI target(s), however, had not been known for a long time. The first clues to the targets of LPI appeared in early 2000, when patents from two pharmaceutical companies (Astrazeneca and Glaxo Smith Kline) indicated that GPR55 responded to certain cannabinoid agonists, raising the possibility that GPR55 is the third cannabinoid receptor after cannabinoid receptors 1 and 2 (CB1 and CB2).[21,22] The endogenous ligands for cannabinoid receptors are 2-arachidonylglycerol (2-AG) and anandamide (Fig. 4), but GPR55 was later shown not to respond to 2-AG or anandamide. Today, GPR55 is not recognized as an endocannabinoid (endogenous cannabinoid) receptor.[23] GPR55 shares homology at the amino acid and nucleic acid levels with the lysophosphatidic acid (LPA) receptors, $LPA_4$/P2Y9, $LPA_5$/GPR92, and $LPA_6$/P2Y5, and the lysophosphatidylserine (LysoPS) receptors, $LPS_1$/GPR34, $LPS_2$/P2Y10, and $LPS_3$/GPR174 (Fig. 2).[24] Therefore, from a structural point of view, it is reasonable that GPR55 recognizes LPI, which is a kind of LPL. However, the pathway and enzymes involved in LPI production are not known. As described below, LPLs other than LPI also activate GPR55. Therefore, even though many reports have confirmed the activation of GPR55 by LPI, it must be said that the true GPR55 endogenous ligand has not yet been identified.

**Properties of GPR55** GPR55 is widely distributed in various organs in both human and mouse but is most strongly expressed in the brain and immune system. Several studies have shown that GPR55 couples mainly with Gα13.[25] GPR55

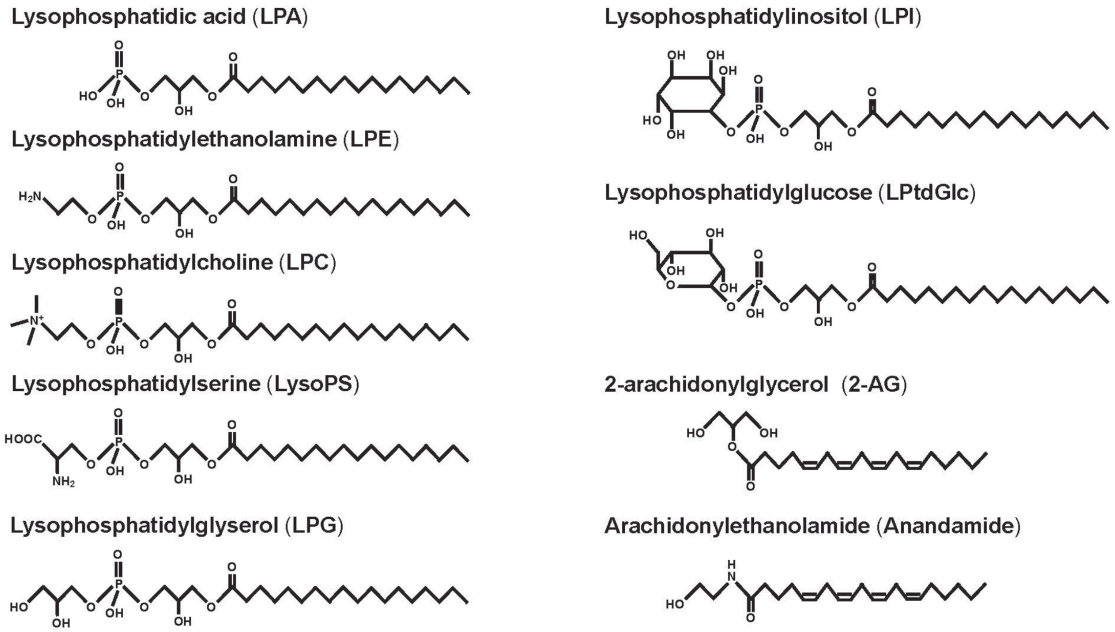


**Fig. 4.** Structures of Lysophospholipids (LPLs) and Endogenous Ligands for Cannabinoid Receptors

Chemical structures of various LPLs are shown. LPLs are composed of about 1000 molecular species in living organisms due to their diversity of polar head groups and fatty acids. 2-AG and anandamide, which have similar structures to LPLs, have been reported as intrinsic ligands for cannabinoid receptors CB1 and CB2. It is now known that they are not ligands for GPR55.

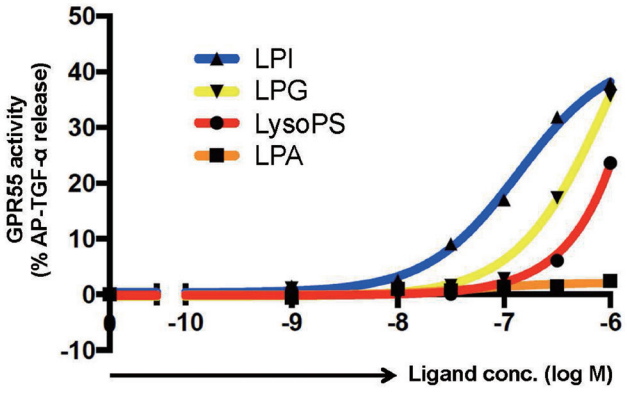


**Fig. 5.** GPR55 Is Activated by Various Lysophospholipids

TGF-α shedding assay was used to evaluate GPR55 activation. The x-axis shows the concentration of each lysophospholipid ligand. The y-axis shows the percentage of AP-TGF-α release as a result of GPR55 activation, which corresponds to the degree of activation. GPR55 responds relatively strongly to LPI and LPG and weakly to LysoPS, but not to LPA.

has been reported to respond not only to LPI but also to LPLs with phosphosugars such as lysophosphatidylglucose (LPtdGlc) and lysophosphatidylglycerol (LPG).[26,27] Our in-house data suggest that GPR55 also weakly responds to lysophosphatidylserine (LysoPS) (Fig. 5). Thus, it is likely that the polar head recognition by GPR55 is not as strict as that of other receptors for LPA and LysoPS. This is another reason why the endogenous ligand for GPR55 is unknown. Sugiura *et al.*[27] reported that the activation of GPR55 was greatly affected by the fatty acid portion of LPI. They showed that GPR55 strongly responds to 2-arachidonyl-LPI, which has arachidonic acid at the *sn*-2 position of the glycerol backbone. This ligand specificity of GPR55 provides a clue to the LPI production system. The same group proposed intracellular $PLA_1$ (DDHD1) as a candidate 2-arachidonyl-LPI-producing enzyme.[8] Removal of the polar head of 2-arachidonyl-LPI (phosphoinositol), yields 2-arachidonylglycerol (2-AG). 2-AG is an endogenous ligand for the cannabinoid receptors CB1 and CB2. It is an interesting idea that 2-arachidonyl-LPI functions as a GPR55 ligand and is then hydrolyzed to 2-AG to act as a CB1/2 ligand.

**Non-Immune Roles of GPR55 Signaling** GPR55 KO mice have a variety of phenotypes. One is a reduced sensitivity to mechanical hyperalgesia,[28] which was observed in both the adjuvant-induced inflammatory and partial nerve ligation-induced neuropathic pain model. Particularly in the inflammatory model, the expressions of some cytokines were found to be variable. Gut *et al.*[26] reported that abnormal axon elongation was observed in developing brain in GPR55-deficient mice, and GPR55 was responsible for ligand-repulsive axon guidance in nociceptive, pain-sensitive neurons. They proposed that LPtdGlc was produced by radial glia and served as a ligand for GPR55.

**Roles of GPR55 Signaling in Cancer** GPR55 appears to be deeply involved in the progression of cancer. GEPIA2 (Gene Expression Profiling Interactive Analysis, using data from TCGA and GTEx), which is a gene expression database of cancer tissue, was used to examine the association between GPR55 and cancer. Among patients with myeloid leukemia (n=106), the top 25% (n=27) with high expression of GPR55 in bone marrow cell samples had significantly lower survival rates than the bottom 75% (n=79) (Fig. 6).[29] Other analysis of clinical samples from human cancer patients also suggested that GPR55 expression correlated with cancer progression in

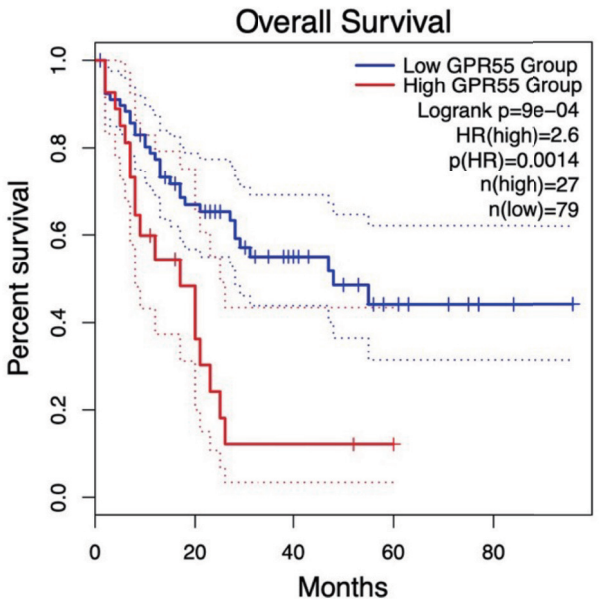


**Fig. 6.** Overall Survival Curves of AML Patients Based on Levels of GPR55 Expression

The Kaplan-Meier curve is drawn using the GEPIA2 online resource. Bone marrow samples of AML from the TCGA and the GTEx projects are used in this analysis. Group cutoff is defined as the top 25% with high GPR55 expression.

several cancer types. For example, in breast tumors, pancreatic tumors, and glioblastomas, GPR55 expression was positively correlated with poor prognosis and cancer progression.[30,31] Indeed, some *in vivo* mouse models showed that GPR55 had a role in tumorigenesis.[31,32] In azoxymethane and dextran sodium sulfate (DSS)-induced colorectal cancer models, GPR55-deficient mice showed significantly reduced colorectal cancer development. GPR55 has also been reported to stimulate cell proliferation *in vitro*[31,33,34] and promotes metastasis *in vivo*.[30,35] Thus, many reports agree that GPR55 generally promotes the progression of cancer. Most studies of GPR55 have been about its function in cancer cells.[36,37]

**Roles of GPR55 Signaling in the Immune System** As mentioned above, expression of GPR55 in cancer cells is thought to play an important role in cancer progression. GPR55 is also expressed on immune cells where it has some unique functions. Here, we describe the functions of GPR55 in myeloid and lymphoid cells.

GPR55 has been reported to function in human and mouse myeloid cells. In human mast cells, GPR55 is involved in chemotaxis by its ability to recognize the chemical gradient of LPI.[38] As in mast cells, LPI promotes migration of human monocytes and macrophages via GPR55.[39] GPR55 also promotes and inhibits the production of proinflammatory cytokines in mouse macrophages.[40,41]

GPR55 also regulates lymphocyte function as well as myeloid cells. Sumida *et al.*[42] suggested that GPR55 functions in intraepithelial lymphocytes (IELs) because loss of GPR55 in γδ T cells (a T cell subset abundant in IELs) accelerated their migration in intestine, possibly as a result of their reduced interaction with the surrounding epithelial cells. They concluded that GPR55 signaling in γδ T cells of IELs enhances drug-induced intestinal injury in the small intestine by suppressing the immune response. Guillamat-Prats *et al.*[43] showed that GPR55 promoted the differentiation and maturation of B cells into plasma cells. GPR55-deficient mice showed a disrupted structure of the germinal center in the spleen, suggesting that GPR55 signaling is an important determinant of B cell differentiation. As a result, GPR55 suppressed excessive activation of B cells, thereby suppressing development of atherosclerosis.

**Conclusion** This review briefly summarized the general characteristics of LPI and its receptor, GPR55, as well as its biological and pathological functions. To date, LPI has been postulated as an endogenous ligand for GPR55. However, GPR55 is also activated by lysophospholipids other than LPI. Thus, the true GPR55 ligand remains unknown, and further detailed analyses are needed. As for GPR55, several reports have shown that it is expressed in immune cells as well as in cancer cells and exhibits various functions in diverse manners. The studies on immunological functions of GPR55 have just started, and this field could be an area attracting more attention from researchers in the future.

**Conflict of interest** The authors declare no conflict of interest.

## REFERENCES

1) Burke JE, Dennis EA. Phospholipase A2 biochemistry. *Cardiovasc. Drugs Ther.*, **23**, 49–59 (2009).
2) Yaginuma S, Kawana H, Aoki J. Current Knowledge on Mammalian Phospholipase A1, Brief History, Structures, Biochemical and Pathophysiological Roles. *Molecules*, **27**, 2487 (2022).
3) Ali G, Chishti MS, Raza SI, John P, Ahmad W. A mutation in the lipase H (LIPH) gene underlie autosomal recessive hypotrichosis. *Hum. Genet.*, **121**, 319–325 (2007).
4) Kazantseva A, Goltsov A, Zinchenko R, Grigorenko AP, Abrukova AV, Moliaka YK, Kirillov AG, Guo Z, Lyle S, Ginter EK, Rogaev EI. Human Hair Growth Deficiency Is Linked to a Genetic Defect in the Phospholipase Gene *LIPH*. *Science*, **314**, 982–985 (2006).
5) Takagi Y, Nishikado S, Omi J, Aoki J. The Many Roles of Lysophospholipid Mediators and Japanese Contributions to This Field. *Biol. Pharm. Bull.*, **45**, 1008–1021 (2022).
6) Aoki J, Taira A, Takanezawa Y, Kishi Y, Hama K, Kishimoto T, Mizuno K, Saku K, Taguchi R, Arai H. Serum Lysophosphatidic Acid Is Produced through Diverse Phospholipase Pathways *. *J. Biol. Chem.*, **277**, 48737–48744 (2002).
7) Ginsberg HN. LIPOPROTEIN PHYSIOLOGY. *Endocrinol. Metab. Clin.*, **27**, 503–519 (1998).
8) Yamashita A, Kumazawa T, Koga H, Suzuki N, Oka S, Sugiura T. Generation of lysophosphatidylinositol by DDHD domain containing 1 (DDHD1): possible involvement of phospholipase D/phosphatidic acid in the activation of DDHD1. *Biochimica et Biophysica Acta (BBA) -. Mol. Cell Biol. Lipids*, **1801**, 711–720 (2010).
9) Alonso T, Santos E. Increased intracellular glycerophosphoinositol is a biochemical marker for transformation by membrane-associated and cytoplasmic oncogenes. *Biochem. Biophys. Res. Commun.*, **171**, 14–19 (1990).
10) Falasca M, Corda D. Elevated levels and mitogenic activity of lysophosphatidylinositol in k-ras-transformed epithelial cells. *Eur. J. Biochem.*, **221**, 383–389 (1994).
11) Xiao Y, Chen Y, Kennedy AW, Belinson J, Xu Y. Evaluation of Plasma Lysophospholipids for Diagnostic Significance Using Electrospray Ionization Mass Spectrometry (ESI-MS) Analyses. *Ann. N. Y. Acad. Sci.*, **905**, 242–259 (2000).
12) Sutphen R, Xu Y, Wilbanks GD, Fiorica J, Grendys EC Jr, LaPolla JP, Arango H, Hoffman MS, Martino M, Wakeley K, Griffin D, Blanco RW, Cantor AB, Xiao Y, Krischer JP. Lysophospholipids Are Potential Biomarkers of Ovarian Cancer. *Cancer Epidemiol. Biomarkers Prev.*, **13**, 1185–1191 (2004).
13) Lee GB, Lee JC, Moon MH. Plasma lipid profile comparison of five

different cancers by nanoflow ultrahigh performance liquid chromatography-tandem mass spectrometry. *Anal. Chim. Acta*, **1063**, 117–126 (2019).
14) Kitamura C, Sonoda H, Nozawa H, Kano K, Emoto S, Murono K, Kaneko M, Hiyoshi M, Sasaki K, Nishikawa T, Shuno Y, Tanaka T, Hata K, Kawai K, Aoki J, Ishihara S. The component changes of lysophospholipid mediators in colorectal cancer. *Tumour Biol.*, **41**, 101042831984861 (2019).
15) Wang Y, Hinz S, Uckermann O, Hönscheid P, Von Schönfels W, Burmeister G, Hendricks A, Ackerman JM, Baretton GB, Hampe J, Brosch M, Schafmayer C, Shevchenko A, Zeissig S. Shotgun lipidomics-based characterization of the landscape of lipid metabolism in colorectal cancer. *Biochimica et Biophysica Acta (BBA) -. Mol. Cell Biol. Lipids*, **1865**, 158579 (2020).
16) Sonoda H, Kitamura C, Kano K, Anzai H, Nagai Y, Abe S, Yokoyama Y, Ishii H, Kishikawa J, Murono K, Emoto S, Sasaki K, Kawai K, Nozawa H, Aoki J, Ishihara S. Changes in Lysophospholipid Components in Ulcerative Colitis and Colitis-associated Cancer. *Anticancer Res.*, **42**, 2461–2468 (2022).
17) Kawashima M, Iwamoto N, Kawaguchi-Sakita N, Sugimoto M, Ueno T, Mikami Y, Terasawa K, Sato T-A, Tanaka K, Shimizu K, Toi M. High-resolution imaging mass spectrometry reveals detailed spatial distribution of phosphatidylinositols in human breast cancer. *Cancer Sci.*, **104**, 1372–1379 (2013).
18) Kawashima M, Tokiwa M, Nishimura T, Kawata Y, Sugimoto M, Kataoka TR, Sakurai T, Iwaisako K, Suzuki E, Hagiwara M, Harris AL, Toi M. High-resolution imaging mass spectrometry combined with transcriptomic analysis identified a link between fatty acid composition of phosphatidylinositols and the immune checkpoint pathway at the primary tumour site of breast cancer. *Br. J. Cancer*, **122**, 245–257 (2020).
19) Koizumi A, Narita S, Nakanishi H, Ishikawa M, Eguchi S, Kimura H, Takasuga S, Huang M, Inoue T, Sasaki J, Yoshioka T, Habuchi T, Sasaki T. Increased fatty acyl saturation of phosphatidylinositol phosphates in prostate cancer progression. *Sci. Rep.*, **9**, 13257 (2019).
20) Hiraide T, Ikegami K, Sakaguchi T, Morita Y, Hayasaka T, Masaki N, Waki M, Sugiyama E, Shinriki S, Takeda M, Shibasaki Y, Miyazaki S, Kikuchi H, Okuyama H, Inoue M, Setou M, Konno H. Accumulation of arachidonic acid-containing phosphatidylinositol at the outer edge of colorectal cancer. *Sci. Rep.*, **6**, 29935 (2016).
21) Wise A, Brown A. Identification of modulators of GPR55 activity, Glaxosmithkline, WO0186305 (2001).
22) Drmota T, Greasley P, T. Groblewski, Screening assays for cannabinoid-ligand-type modulators of GPR55, Astrazeneca, WO2004074844 (2004).
23) Oka S, Nakajima K, Yamashita A, Kishimoto S, Sugiura T. Identification of GPR55 as a lysophosphatidylinositol receptor. *Biochem. Biophys. Res. Commun.*, **362**, 928–934 (2007).
24) Makide K, Uwamizu A, Shinjo Y, Ishiguro J, Okutani M, Inoue A, Aoki J. Novel lysophosphoplipid receptors: their structure and function. *J. Lipid Res.*, **55**, 1986–1995 (2014).
25) Inoue A, Ishiguro J, Kitamura H, Arima N, Okutani M, Shuto A, Higashiyama S, Ohwada T, Arai H, Makide K, Aoki J. TGFα shedding assay: an accurate and versatile method for detecting GPCR activation. *Nat. Methods*, **9**, 1021–1029 (2012).
26) Adam T. Guy, Yasuko Nagatsuka, Ooashi N, Inoue M, Nakata A, Greimel P, Inoue A, Nabetani T, Murayama A, Ohta K, Ito Y, Aoki J, Hirabayashi Y, Kamiguchi H. Glycerophospholipid regulation of modality-specific sensory axon guidance in the spinal cord. *Science*, **349**, 974–977 (2015).
27) Oka S, Toshida T, Maruyama K, Nakajima K, Yamashita A, Sugiura T. 2-Arachidonoyl-sn-glycero-3-phosphoinositol: A Possible Natural Ligand for GPR55. *J. Biochem.*, **145**, 13–20 (2009).
28) Staton PC, Hatcher JP, Walker DJ, Morrison AD, Shapland EM, Hughes JP, Chong E, Mander PK, Green PJ, Billinton A, Fulleylove M, Lancaster HC, Smith JC, Bailey LT, Wise A, Brown AJ, Richardson JC, Chessell IP. The putative cannabinoid receptor GPR55 plays a role in mechanical hyperalgesia associated with inflammatory and neuropathic pain. *Pain*, **139**, 225 (2008).
29) Tang Z, Kang B, Li C, Chen T, Zhang Z. GEPIA2: an enhanced web server for large-scale expression profiling and interactive analysis. *Nucleic Acids Res.*, **47**, W556–W560 (2019).
30) Andradas C, Blasco-Benito S, Castillo-Lluva S, Dillenburg-Pilla P, Diez-Alarcia R, Juanes-García A, García-Taboada E, Hernando-Llorente R, Soriano J, Hamann S, Wenners A, Alkatout I, Klapper W, Rocken C, Bauer M, Arnold N, Quintanilla M, Megías D, Vicente-Manzanares M, Urigüen L, Gutkind JS, Guzmán M, Pérez-Gómez E, Sánchez C. Activation of the orphan receptor GPR55 by lysophosphatidylinositol promotes metastasis in triple-negative breast cancer. *Oncotarget*, **7**, 47565–47575 (2016).
31) Andradas C, Caffarel MM, Pérez-Gómez E, Salazar M, Lorente M, Velasco G, Guzmán M, Sánchez C. The orphan G protein-coupled receptor GPR55 promotes cancer cell proliferation via ERK. *Oncogene*, **30**, 245–252 (2011).
32) Hasenoehrl C, Feuersinger D, Sturm EM, Bärnthaler T, Heitzer E, Graf R, Grill M, Pichler M, Beck S, Butcher L, Thomas D, Ferreirós N, Schuligoi R, Schweiger C, Haybaeck J, Schicho R. G protein-coupled receptor GPR55 promotes colorectal cancer and has opposing effects to cannabinoid receptor 1. *Int. J. Cancer*, **142**, 121–132 (2018).
33) Piñeiro R, Maffucci T, Falasca M. The putative cannabinoid receptor GPR55 defines a novel autocrine loop in cancer cell proliferation. *Oncogene*, **30**, 142–152 (2011).
34) Hu G, Ren G, Shi Y. The putative cannabinoid receptor GPR55 promotes cancer cell proliferation. *Oncogene*, **30**, 139–141 (2011).
35) Kargl J, Andersen L, Hasenöhrl C, Feuersinger D, Stančić A, Fauland A, Magnes C, El-Heliebi A, Lax S, Uranitsch S, Haybaeck J, Heinemann A, Schicho R. GPR55 promotes migration and adhesion of colon cancer cells indicating a role in metastasis. *Br. J. Pharmacol.*, **173**, 142–154 (2016).
36) Falasca M, Ferro R. Role of the lysophosphatidylinositol/GPR55 axis in cancer. *Adv. Biol. Regul.*, **60**, 88–93 (2016).
37) Calvillo-Robledo A, Cervantes-Villagrana RD, Morales P, Marichal-Cancino BA. The oncogenic lysophosphatidylinositol (LPI)/GPR55 signaling. *Life Sci.*, **301**, 120596 (2022).
38) Martínez-Aguilar LM, Ibarra-Sánchez A, Guerrero-Morán DJ, Macías-Silva M, Muñoz-Bello JO, Padilla A, Lizano M, González-Espinosa C. Lysophosphatidylinositol Promotes Chemotaxis and Cytokine Synthesis in Mast Cells with Differential Participation of GPR55 and CB2 Receptors. *Int. J. Mol. Sci.*, **24**, 6316 (2023).
39) Li X, Hanafusa K, Kage M, Yokoyama N, Nakayama H, Hotta T, Oshima E, Kano K, Matsuo I, Nagatsuka Y, Takamori K, Ogawa H, Hirabayashi Y, Iwabuchi K. Lysophosphatidylglucoside is a GPR55 -mediated chemotactic molecule for human monocytes and macrophages. *Biochem. Biophys. Res. Commun.*, **569**, 86–92 (2021).
40) Kurano M, Kobayashi T, Sakai E, Tsukamoto K, Yatomi Y. Lysophosphatidylinositol, especially albumin-bound form, induces inflammatory cytokines in macrophages. *FASEB J.*, **35**, e21673 (2021).
41) Masquelier J, Alhouayek M, Terrasi R, Bottemanne P, Paquot A, Muccioli GG. Lysophosphatidylinositols in inflammation and macrophage activation: altered levels and anti-inflammatory effects. *Biochimica et Biophysica Acta (BBA) -. Mol. Cell Biol. Lipids*, **1863**, 1458–1468 (2018).
42) Sumida H, Lu E, Chen H, Yang Q, Mackie K, Cyster JG. GPR55 regulates intraepithelial lymphocyte migration dynamics and susceptibility to intestinal damage. *Sci. Immunol.*, **2**, eaao1135 (2017).
43) Guillamat-Prats R, Hering D, Derle A, Rami M, Härdtner C, Santovito D, Rinne P, Bindila L, Hristov M, Pagano S, Vuilleumier N, Schmid S, Janjic A, Enard W, Weber C, Maegdefessel L, Faussner A, Hilgendorf I, Steffens S. GPR55 in B cells limits atherosclerosis development and regulates plasma cell maturation. *Nat. Cardiovasc. Res.*, **1**, 1056–1071 (2022).