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Commentary

Lysophosphatidylcholine as a ligand for immunoregulation

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Abstract

Despite the recognized effects of lysophosphatidylcholine upon cells of the immune system and its association with inflammatory processes, its mechanism of action has remained poorly characterized. Our recent identification of the first lysophosphatidylcholine receptor as an immunoregulatory G protein-coupled receptor named G2A whose genetic ablation results in the development of inflammatory autoimmune disease has, therefore, provided a new perspective on the role of this lysophospholipid as a modulator of immune responses. This commentary discusses the biological properties of lysophosphatidylcholine as an immunoregulatory ligand for cells of the innate and adaptive arms of the immune system. Although we focus primarily on ligand interactions with G2A, we also discuss the issue of possible functional redundancy with other receptors with recently established ligand specificities towards phosphorylcholine-containing lysolipids including lysophosphatidylcholine. © 2002 Published by Elsevier Science Inc.

Keywords: Lysophosphatidylcholine; Phospholipase A_2; Oxidized low density lipoprotein; Inflammation; Immune regulation; Systemic autoimmune disease

1. Lysophospholipids

Bioactive lysophospholipids are a group of naturally occurring lipids regulating a wide variety of cellular activities including proliferation, smooth muscle contraction, wound healing, and tumor cell invasiveness [1]. Formation of lysophospholipids is enhanced under inflammatory conditions, in ischemic tissue, and during oxidation of LDL. Lysophosphatidic acid and sphingosine-1-phosphate are the best characterized lysophospholipids, and eight receptors (Endothelial Differentiation Gene receptors; EDG) have been identified thus far with varying ligand specificities towards them [2]. Although most EDG receptors are broadly expressed and mediate the diverse effects of lysophosphatidic acid and sphingosine-1-phosphate in multiple tissues, others such as EDG 6 are expressed predominantly in lymphocytes and accessory immune cells [3], suggesting that their primary roles may be immunoregulatory. However, for certain lysophospholipids, biological actions have been established primarily within the immune system. For example, LPC is an important inflammatory mediator with recognized effects in multiple immune cell types and pathophysiological processes. Most notably, as a major component of oxLDL, LPC plays a major etiological role in atherosclerosis [4]. Oxidative modification of phospholipids is associated with the acute phase response and chronic inflammation, and its by-products are increasingly recognized as key factors in the initiation and progression of chronic inflammatory autoimmune diseases [5–7]. Among these, LPC is implicated in the pathogenesis of the autoimmune disease SLE [8,9].

2. Biological actions of LPC

Molecular species of LPC, distinguished by the lengths and saturation of their acyl chains, are produced from cell membrane-derived phosphatidylcholine (PC) as a result of hydrolysis by PLA_2 [10]. PLA_2 activation is a rate-limiting event in the production of several proinflammatory lipids (Fig. 1) and is associated with cellular responses to multi-

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Abbreviations: APCs, antigen presenting cells; GPCR, G protein-coupled receptor; LDL, low-density lipoprotein; LPC, lysophosphatidylcholine; oxLDL, oxidized low-density lipoprotein; PLA_2, phospholipase A_2; SLE, systemic lupus erythematosus; and SPC, sphingosylphosphorylcholine.

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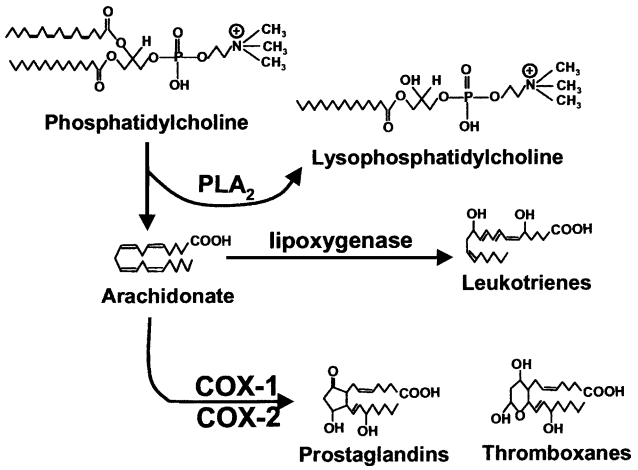

Fig. 1. Phospholipase A_2 (PLA_2), a rate-limiting enzyme in the generation of multiple lipid inflammatory mediators. A large proportion of cellular membrane phosphatidylcholine contains an arachidonyl acyl moiety at the *sn*-2 position, the target of PLA_2 hydrolysis. Consequently, in addition to lysophosphatidylcholine, arachidonic acid is a major product of PLA_2 action. Arachidonic acid is a key intermediate for the production of various other lipids via the actions of lipoxygenase and cyclooxygenase (COX) enzymes. COX-2 is a transcriptionally regulated isoform of COX induced by multiple mitogenic and stress stimuli, and the target of highly efficacious inhibitory drugs used in the treatment of chronic inflammatory conditions.

ple stimuli, including stress and inflammatory signals. Among the different forms of PLA_2, secretory forms ($sPLA_2$) are released from macrophages and other cell types at sites of inflammation and tissue injury [11]. LPC is also derived from PC-containing lipoproteins as a result of oxidative processes via activation of endogenous PLA_2 [12]. Early studies demonstrating the ability of high concentrations of LPC (50 μM) to modulate plasma membrane integrity via micelle formation suggested that its biological role may be primarily structural and cytolytic. However, specific effects of low concentrations of LPC at the level of several physiological and pathological processes through an uncharacterized GPCR(s) have since been widely reported. Extracellular production of LPC by $sPLA_2$ promotes inflammatory effects including up-regulation of endothelial cell adhesion molecules and growth factors [13,14], chemotaxis of monocytes and T lymphocytes [15,16], and stimulation of macrophage activation [17]. Although some effects of LPC were believed to be mediated by platelet-activating factor (PAF) receptors in certain cell types [18], the identification of a specific high-affinity LPC receptor remained elusive. We have recently identified two LPC receptors, one of which plays an important immunoregulatory role and exhibits higher affinity binding to this lysophospholipid [19–21].

3. LPC receptors

We identified G2A, a G protein-coupled receptor, as a transcriptional target of the leukemogenic tyrosine kinase BCR-ABL in murine B lymphoid progenitor cells [22].

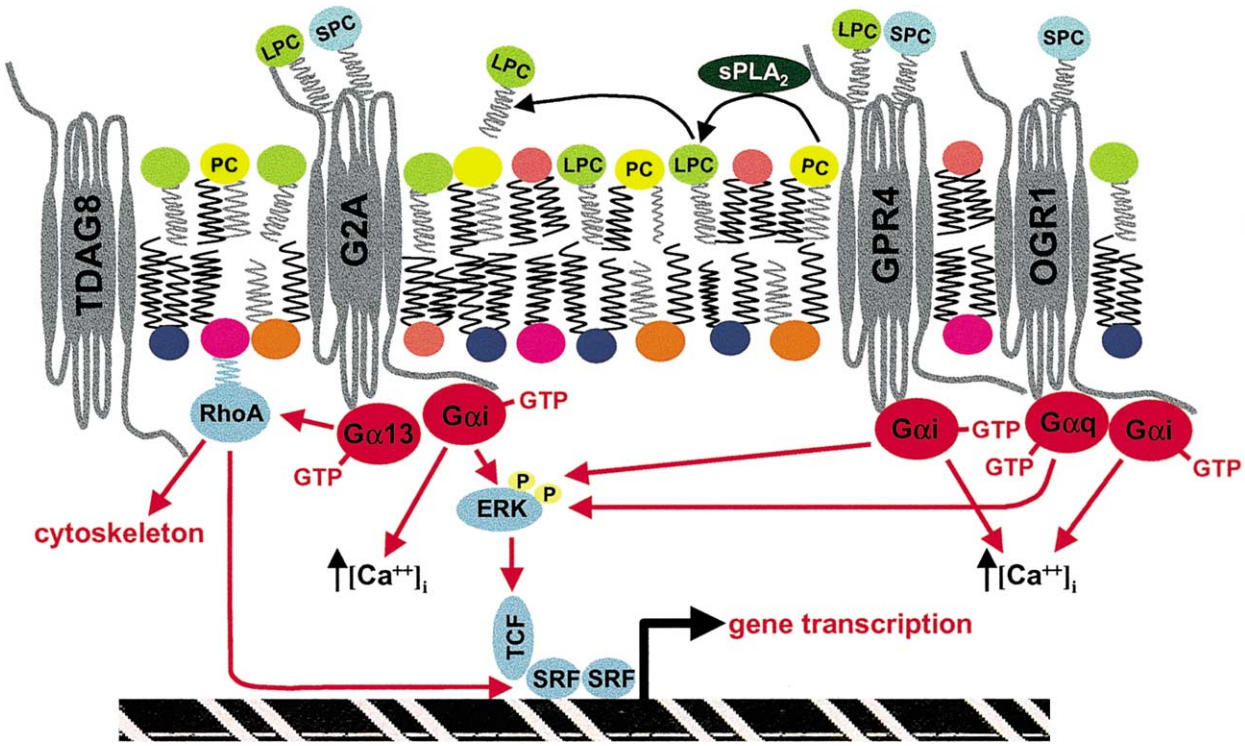

Fig. 2. Overlapping ligand specificities of G2A and its relatives for lysophosphatidylcholine (LPC) and/or sphingosylphosphorylcholine (SPC). G2A elicits RhoA-dependent actin cytoskeleton rearrangement and transcriptional activation of serum response factor (SRF) via Gα13 heterotrimeric G proteins. G2A, GPR4, and OGR1 mediate ERK MAP kinase activation and intracellular calcium increase ($\uparrow[Ca^{2+}]_i$) via Gαi and/or Gαq heterotrimeric G proteins [19,21,29].

While G2A is expressed predominantly in hematopoietic cells including T lymphocytes, it is also transcriptionally induced in response to stress stimuli in B lymphoid cells. G2A couples to Gα13 heterotrimeric G proteins to activate RhoA, leading to the assembly of actin stress fibers and transcriptional activation of serum response factor [23,24]. Although studies of biological and signaling events downstream of G2A suggested that transcriptional induction of this GPCR may function at the level of the actin cytoskeleton to regulate lymphocyte activation/proliferation and/or cellular migration, more recently, genetic ablation of G2A function in mice has revealed a role for G2A in the homeostatic regulation of lymphocyte pools and the maintenance of immunological tolerance. G2A-deficient mice develop a late-onset systemic autoimmune syndrome exhibiting many features in common with the human autoimmune disease SLE, and their T lymphocytes exhibit hyperproliferative responses to antigen receptor stimulation [25].

Based upon protein sequence homology, G2A is closely related to three GPCRs (GPCR 4, GPR 4; ovarian cancer related GPCR 1, OGR 1; and T cell death associated GPCR 8, TDAG 8) [26–28] with overlapping expression in cells of the innate (macrophages and dendritic cells) and adaptive immune systems (Kabarowski JHS, Lim R and Witte ON, unpublished observations). We have identified LPC as a ligand for G2A and established G2A, GPR 4, and OGR 1 as representative members of a receptor family with ligand specificities towards the phosphorylcholine-containing lysophospholipids LPC and SPC [19,21,29]. These receptors mediate intracellular calcium flux and ERK MAP kinase activation in response to their ligands via Gαi or Gαq heterotrimeric G proteins (Fig. 2). Although no direct binding studies have been reported, TDAG 8 is activated by the glycosphingolipid psychosine (D-galactosyl-β-1,1′-sphingosine) and several related lipids [30]. TDAG 8 was originally identified by virtue of its transcriptional induction during thymocyte apoptosis and is also induced in dexamethasone-treated T cells [28]. It is not clear how, if at all, this receptor–ligand pair could modulate physiological apoptotic responses during T lymphocyte development or immune function. However, we do not rule out the possibility that, as for its relatives, TDAG 8 may exhibit broader ligand specificity than that established thus far.

4. Biological forms of LPC

LPC can exist in several physiological forms, including free, micellar, LDL, bound to hydrophobic serum proteins such as albumin, consumed within immune complexes, and incorporated into plasma membranes. While application of LPC elicits short-term responses via G2A and GPR4 [19,21], it is likely that long-term exposure of cells to exogenously applied LPC results in its conversion to a form with altered receptor binding properties. Indeed, physiological concentrations of LPC in body fluids are high (up to 100 μM) and therefore probably exist predominantly in an ''inactive'' form. A large proportion of this LPC is present in association with hydrophobic proteins such as albumin and within lipoprotein complexes that are incapable of eliciting LPC-dependent biological responses [31] including inhibition of T cell proliferation and ERK MAP kinase activation via G2A (Kabarowski JHS and Witte ON, unpublished observations). It is likely, therefore, that the actions of LPC are spatially and temporally constrained, possibly occurring in an autocrine/paracrine fashion. For example, activation of receptors by LPC produced from plasma membranes of neighboring cells may represent one mode of spatially restricted paracrine action. Temporal restriction of LPC action is also likely imposed by the presence of extracellular hydrolytic enzymes capable of converting this lysophospholipid [32]. These are all important considerations with respect to modulation of immunological processes within the highly organized microenvironments of secondary lymphoid organs and at sites of pathogen encounter by macrophage and dendritic cells. Nevertheless, long-range effects of LPC are recognized, but may be restricted to its transport function as a preferred carrier of certain essential fatty acids to specific tissues [33,34].

5. LPC, T lymphocytes, and autoimmunity

Increased levels of antibodies against LPC in patients with SLE [8,9,35] and the development of systemic autoimmune disease in G2A-deficient animals [25] suggest a pathophysiological connection. How the pathology of this disease could relate to this receptor/ligand pair is likely to be complex considering the multiple susceptibility factors involved in SLE [36]. Further complexity is introduced by the broad cellular involvement in SLE and the presence of related LPC receptors in multiple immune cell types. Nevertheless, several possibilities can be proposed. For example, several studies suggest that endogenously produced LPC may influence T cell responses and that receptor-mediated signals are involved. For example, PLA_2-mediated LPC production is stimulated in T cells following antigen receptor (TCR) cross-linking [37] and may modulate long-term responses of activated T lymphocytes in an autocrine/paracrine fashion. Consistent with this hypothesis, a primary defect in young disease-free G2A-deficient mice is a hyperproliferative response of T lymphocytes to antigen receptor stimulation. While this suggests that loss of G2A-dependent growth inhibitory responses of T lymphocytes to LPC may underlie the age-related autoimmune syndrome developing in G2A-deficient mice, pathophysiological involvement for other immune cell types is likely considering the broad cellular involvement in systemic autoimmune disease. Expression

of G2A in macrophages and dendritic cells expands the repertoire of immunological processes in which G2A may function to include innate immune responses and antigen presentation.

6. LPC as a regulator of innate immunity

The innate immune system is the first line of host defense against infectious challenge and subsequently controls the induction of adaptive immune responses via antigen presentation and cytokine production. Dendritic cells and macrophages are the major APCs of the immune system. APCs present antigenic peptides in the context of major histocompatibility complex to naïve T lymphocytes in the initiation of T-dependent immune responses. Monocyte derived and resident dendritic cells take up antigen in peripheral tissues and migrate to T cell areas of draining lymph nodes where interaction of co-stimulatory molecules on the surface of the APC with their cognate T cell expressed molecules results in activation of antigen-specific T lymphocytes [38]. The induction of these co-stimulatory molecules (B7.1,CD80; B7.2,CD86), as well as other key immunoregulatory receptors and cytokines, requires a ''danger signal'' identifying an infectious non-self encounter triggered by recognition of ''pathogen-associated molecular patterns'' such as lipopolysaccharide, bacterial lipoproteins, and bacterial DNA via pattern recognition receptors [39]. Any defect in these processes is likely to deregulate T lymphocyte activation/proliferation and peripheral immunological tolerance.

Therefore, in addition to a direct role for G2A in the modulation of T lymphocyte responses, innate immune responses of macrophages and dendritic cells may be regulated via this receptor in response to local fluctuations in lysolipids encountered during infection and inflammation. It is possible that LPC produced at sites of inflammation and from disintegrating apoptotic/necrotic cell membranes may be a novel ''molecular pattern'' recognized by G2A to modulate innate immune processes and the initiation and/or resolution of inflammatory responses. For example, G2A may relay signals regulating APC migration between tissue and lymph in response to LPC produced at inflammatory sites through its effects on actin cytoskeleton reorganization [23]. On the other hand, APC/T lymphocyte interactions within lymph nodes may be modulated by autocrine/paracrine production of LPC through G2A to influence the threshold for T cell activation.

In addition to the elimination of pathogens, macrophage recruitment to inflammatory sites is critical for the efficient clearance of necrotic cell debris and apoptotic cells. Recognition and uptake of apoptotic cells by macrophages and newly generated bone marrow derived immature dendritic cells are also important for maintaining peripheral tolerance to self-antigens [40]. By ''sampling'' and subsequently presenting self-antigens derived from apoptotic cells, these monocytic derived cells constitute a critical homeostatic mechanism contributing to the suppression of autoreactivity. In addition to alterations in surface expression of phospholipids, their increased oxidation is also a characteristic feature of apoptotic cells, which express oxLDL-specific ligands on their surfaces increasingly recognized as targets of autoantibodies in SLE [41–43]. Indeed, impaired apoptotic clearance can promote the development of autoimmunity, and such a defect can be induced by antibodies against LPC [44,45]. Although increased $sPLA_2$-mediated LPC production in the outer plasma membrane leaflet of injured and apoptotic cells has been suggested to potentiate binding of the acute phase protein C-reactive protein (CRP) leading to complement activation via the classical pathway and their consequent phagocytosis [46], whether increased levels of cellular LPC are a physiological determinant of apoptotic cell recognition via G2A and/or GPR4 receptors is presently unknown.

7. LPC as an etiological factor in atherosclerosis

The key role of LPC as a major antigenic component of oxLDL has implicated this bioactive lipid in atherosclerosis, the primary cause of heart disease and stroke. However, its role is poorly understood. Although monocyte/macrophage recruitment to the arterial endothelium and uptake of proinflammatory oxLDL and apoptotic cells likely serve a protective function, their progressive accumulation in hypercholesterolemic subjects is believed to initiate the development of atherosclerotic lesions. Later stages of lesion development are associated with T lymphocyte infiltration, their immune activation and cytokine production (TH1/TH2), and humoral responses to antigens, most significantly oxLDL epitopes [4]. Indeed, all aspects of immune function discussed thus far as potential targets of LPC action play some role in atherogenesis. Most notably, macrophage responses to oxLDL such as migration and activation are likely determined to a significant extent by its LPC content, and may therefore be mediated to some degree via G2A and/or GPR4. Monocyte recruitment to lesion-prone arterial sites is also regulated by the expression of surface adhesion molecules and chemokines by endothelial cells in response to inflammatory mediators. Among these, intercellular adhesion molecule-1 (ICAM-1) and monocyte chemotactic protein-1 (MCP-1) expression has been shown to be induced in endothelial cells by exposure to LPC [47,48]. Following their recruitment and migration into the subendothelial space, monocytes differentiate into macrophages and take up oxLDL via scavenger receptors, leading to the formation of cholesterol ester loaded ''foam cells.'' Here again, the LPC component of oxLDL is a key mediator of this process via up-regulation of scavenger receptor expression on the surface of macrophages [49]. LPC may even propagate the oxidative

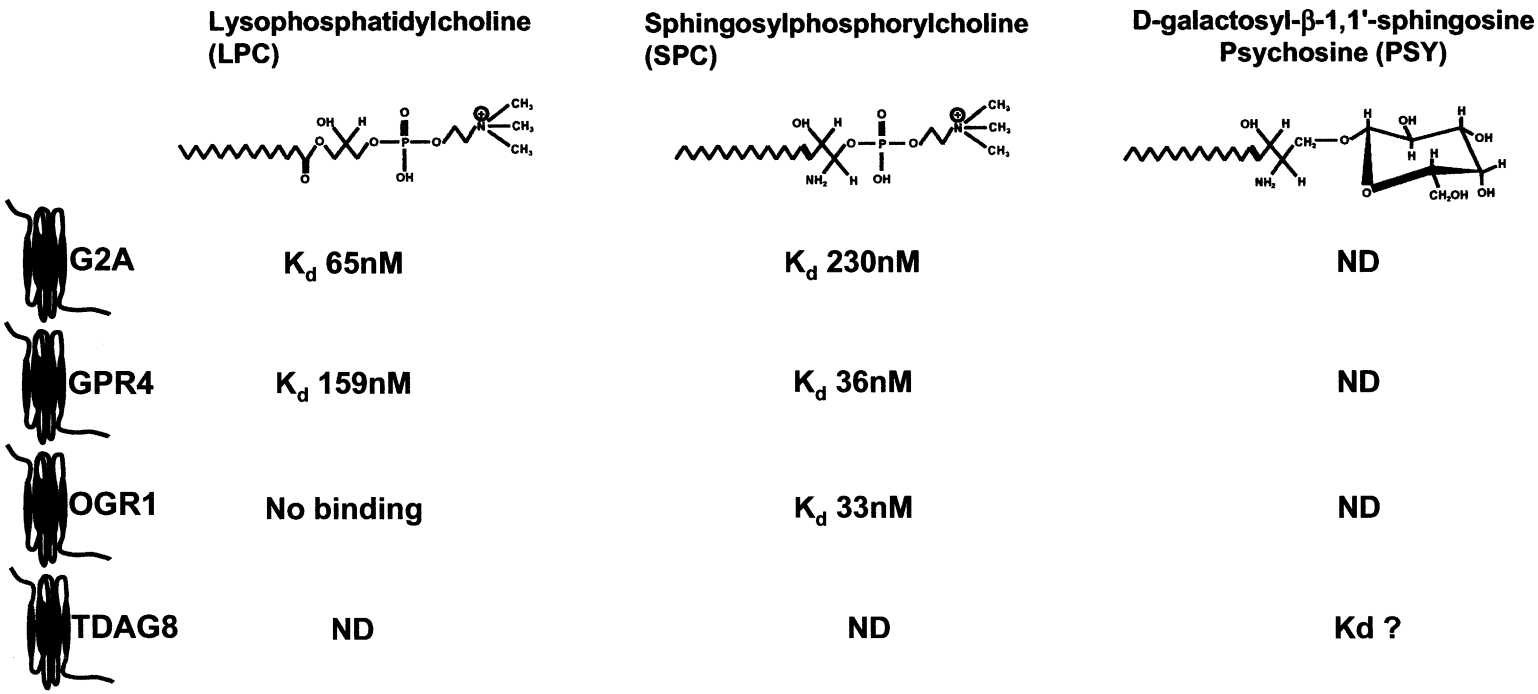

Fig. 3. Ligand binding specificities and affinities of G2A, GPR4, OGR1, and TDAG8. Binding studies were performed on membrane preparations from HEK293 cells overexpressing the indicated receptors [19,21,29]. (ND: not determined; Kd?: no direct binding studies reported.)

processes that lead to the accumulation of oxLDL through its action on endothelial NADH/NADPH oxidase and endothelial/macrophage nitric oxide synthase mediated production of reactive oxygen species [50,51]. Which, if any, of these LPC-dependent cellular events are mediated through G2A and GPR4 are questions currently being addressed in our laboratory. To directly test the pathophysiological role of these receptors in atherogenesis, we are examining the susceptibility of receptor-deficient mice harboring a targeted deletion of the LDL receptor to the development of atherosclerotic lesions.

8. LPC receptors as pharmacological targets

The suitability of GPCRs as targets of drug-based therapeutic intervention promises that further studies of G2A function may uncover clinical benefits of modulating G2A activity in the treatment of chronic inflammatory diseases. The identification of LPC as a ligand for G2A is a major step towards achieving this goal as high throughput screening of chemically modified variants of this lysophospholipid may uncover molecules with agonistic/antagonistic properties towards G2A function. However, receptor/ligand relationships within GPCR families exhibit significant promiscuity, with many receptors recognizing more than one ligand and vice versa. We have found this to be the case for members of the ''G2A receptor sub-family,'' which exhibit both distinct and overlapping expression patterns together with varying ligand binding affinities (Fig. 3). This suggests that these receptors may perform both redundant as well as unique biological roles, which have important implications for the design of pharmacological agents with the potential to selectively agonize or antagonize one or more of them without suppressing or potentiating immunological processes in a global and deleterious manner. In addition, sequence homology comparisons suggest that one or more orphan GPCRs may prove to be additional members of this receptor sub-family (Ferl GZ, Kabarowski JHS, Radu CG, Roy MP and Witte ON, unpublished observations). Nevertheless, the fact that minor alterations of acyl chain length abolish LPC binding to G2A [19] suggests that other structural modifications may uncover ligand mimetics with higher receptor binding affinities sufficient to effectively compete LPC binding.

An alternative approach to modulate receptor function *in vivo* may be through specific targeting with monoclonal antibodies recognizing extracellular epitopes of the ligand binding pocket formed by the packed α-helical transmembrane domains. Irrespective of methodology, however, an understanding of the mechanisms by which loss of G2A function disrupts immunological tolerance to precipitate autoimmunity and the key cellular and biochemical processes impacted by LPC ligation of its receptors in alternative cell types is a prerequisite for the successful employment of any modulatory agent, as well as the design of animal model systems for their preliminary evaluation. We hope our future studies as well as those conducted in other laboratories will lead to opportunities for such clinical applications.

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References

[1] Fukushima N, Ishii I, Contos JJ, Weiner JA, Chun J. Lysophospholipid receptors. Annu Rev Pharmacol Toxicol 2001;41:507–34.
[2] Hla T, Lee MJ, Ancellin N, Paik JH, Kluk MJ. Lysophospholipids—receptor revelations. Science 2001;294:1875–8.
[3] Graler MH, Bernhardt G, Lipp M. EDG6, a novel G-protein-coupled receptor related to receptors for bioactive lysophospholipids, is specifically expressed in lymphoid tissue. Genomics 1998;53:164–9.
[4] Lusis AJ. Atherosclerosis. Nature 2000;407:233–41.
[5] Romero FI, Khamashta MA, Hughes GR. Lipoprotein(a) oxidation and autoantibodies: a new path in atherothrombosis. Lupus 2000;9:206–9.
[6] Iuliano L, Pratico D, Ferro D, Pittoni V, Valesini G, Lawson J, FitzGerald GA, Violi F. Enhanced lipid peroxidation in patients positive for antiphospholipid antibodies. Blood 1997;90:3931–5.
[7] Koh JS, Wang Z, Levine JS. Cytokine dysregulation induced by apoptotic cells is a shared characteristic of murine lupus. J Immunol 2000;165:4190–201.
[8] Wu R, Svenungsson E, Gunnarsson I, Andersson B, Lundberg I, Schafer Elinder L, Frostegard J. Antibodies against lysophosphatidylcholine and oxidized LDL in patients with SLE. Lupus 1999;8:142–50.
[9] Wu R, Svenungsson E, Gunnarsson I, Haegerstrand-Gillis C, Andersson B, Lundberg I, Elinder LS, Frostegård J. Antibodies to adult human endothelial cells cross-react with oxidized low-density lipoprotein and β_2-glycoprotein I (β_2-GPI) in systemic lupus erythematosus. Clin Exp Immunol 1999;115:561–6.
[10] McKean ML, Smith JB, Silver MJ. Formation of lysophosphatidylcholine by human platelets in response to thrombin. Support for the phospholipase A_2 pathway for the liberation of arachidonic acid. J Biol Chem 1981;256:1522–4.
[11] Bingham III CO, Austen KF. Phospholipase A_2 enzymes in eicosanoid generation. Proc Assoc Am Physicians 1999;111:516–24.
[12] Chisolm GM, Penn MS. Oxidized lipoproteins and atherosclerosis. In: Fuster V, Ross R, Topol E, editors. Atherosclerosis and coronary disease. New York: Raven Press, 1996. p. 129–49.
[13] Kume N, Gimbrone Jr MA. Lysophosphatidylcholine transcriptionally induces growth factor gene expression in cultured human endothelial cells. J Clin Invest 1994;93:907–11.
[14] Kume N, Cybulsky MI, Gimbrone Jr MA. Lysophosphatidylcholine, a component of atherogenic lipoproteins, induces mononuclear leukocyte adhesion molecules in cultured human and rabbit arterial endothelial cells. J Clin Invest 1992;90:1138–44.
[15] Quinn MT, Parthasarathy S, Steinberg D. Lysophosphatidylcholine: a chemotactic factor for human monocytes and its potential role in atherogenesis. Proc Natl Acad Sci USA 1988;85:2805–9.

[16] McMurray HF, Parthasarathy S, Steinberg D. Oxidatively modified low density lipoprotein is a chemoattractant for human T lymphocytes. J Clin Invest 1993;92:1004–8.
[17] Yamamoto N, Homma S, Millman I. Identification of the serum factor required for in vitro activation of macrophages. Role of vitamin D_3-binding protein (group specific component, Gc) in lysophospholipid activation of mouse peritoneal macrophages. J Immunol 1991;147: 273–80.
[18] Huang YH, Schäfer-Elinder L, Wu R, Claesson HE, Frostegård J. Lysophosphatidylcholine (LPC) induces proinflammatory cytokines by a platelet-activating factor (PAF) receptor-dependent mechanism. Clin Exp Immunol 1999;116:326–31.
[19] Kabarowski JHS, Zhu K, Le LQ, Witte ON, Xu Y. Lysophosphatidylcholine as a ligand for the immunoregulatory receptor G2A. Science 2001;293:702–5.
[20] Carson MJ, Lo D. Immunology. The push-me pull-you of T cell activation. Science 2001;293:618–9.
[21] Zhu K, Baudhuin LM, Hong G, Williams FS, Cristina KL, Kabarowski JHS, Witte ON, Xu Y. Sphingosylphosphorylcholine and lysophosphatidylcholine are ligands for the G protein-coupled receptor GPR4. J Biol Chem 2001;276:41325–35.
[22] Weng Z, Fluckiger AC, Nisitani S, Wahl MI, Le LQ, Hunter CA, Fernal AA, Le Beau MM, Witte ON. A DNA damage and stress inducible G protein-coupled receptor blocks cells in G_2/M. Proc Natl Acad Sci USA 1998;95:12334–9.
[23] Kabarowski JHS, Feramisco JD, Le LQ, Gu JL, Luoh SW, Simon MI, Witte ON. Direct genetic demonstration of Gα13 coupling to the orphan G protein-coupled receptor G2A leading to Rho-A-dependent actin rearrangement. Proc Natl Acad Sci USA 2000;97:12109–14.
[24] Zohn IE, Klinger M, Karp X, Kirk H, Symons M, Chrzanowska-Wodnicka M, Der CJ, Kay RJ. G2A is an oncogenic G protein-coupled receptor. Oncogene 2000;19:3866–77.
[25] Le LQ, Kabarowski JHS, Weng Z, Satterthwaite AB, Harvill ET, Jensen ER, Miller JF, Witte ON. Mice lacking the orphan G protein-coupled receptor, G2A, develop a late-onset autoimmune syndrome. Immunity 2001;14:561–71.
[26] Heiber M, Docherty JM, Shah G, Nguyen T, Cheng R, Heng HHQ, Marchese A, Tsui L-C, Shi X, George SR, O'Dowd BF. Isolation of three novel human genes encoding G protein-coupled receptors. DNA Cell Biol 1995;14:25–35.
[27] Xu Y, Casey G. Identification of human OGR1, a novel G protein-coupled receptor that maps to chromosome 14. Genomics 1996;5:397–402.
[28] Choi J-W, Lee SY, Choi Y. Identification of a putative G protein-coupled receptor induced during activation-induced apoptosis of T cells. Cell Immunol 1996;168:78–84.
[29] Xu Y, Zhu K, Hong G, Wu W, Baudhuin LM, Xiao Y, Damron DS. Sphingosylphosphorylcholine is a ligand for ovarian cancer G-protein-coupled receptor 1. Nat Cell Biol 2000;2:261–7.
[30] Im DS, Heise CE, Nguyen T, O'Dowd BF, Lynch KR. Identification of a molecular target of psychosine and its role in globoid cell formation. J Cell Biol 2001;153:429–34.
[31] Vuong TD, de Kimpe S, de Roos R, Rabelink TJ, Koomans HA, Joles JA. Albumin restores lysophosphatidylcholine-induced inhibition of vasodilation in rat aorta. Kidney Int 2001;60:1088–96.
[32] Tokumura A, Yamano S, Aono T, Fukuzawa K. Lysophosphatidic acids produced by lysophospholipase D in mammalian serum and body fluid. Ann NY Acad Sci 2000;905:347–50.
[33] Brossard N, Croset M, Normand S, Pousin J, Lecerf J, Laville M, Tayot JL, Lagarde M. Human plasma albumin transports [^{13}C]-docosahexaenoic acid in two lipid forms to blood cells. J Lipid Res 1997;38:1571–82.
[34] Lagarde M, Bernoud N, Brossard N, Lemaitre-Delaunay D, Thies F, Croset M, Lecerf J. Lysophosphatidylcholine as a preferred carrier form of docosahexaenoic acid to the brain. J Mol Neurosci 2001;16:201–21.
[35] George J, Harats D, Gilburd B, Levy Y, Langevitz P, Shoenfeld Y. Atherosclerosis-related markers in systemic lupus erythematosus patients: the role of humoral immunity in enhanced atherogenesis. Lupus 1999;8:220–6.
[36] Sullivan KE. Genetics of systemic lupus erythematosus. Clinical implications. Rheum Dis Clin North Am 2000;26:229–56.
[37] Asaoka Y, Oka M, Yoshida K, Sasaki Y, Nishizuka Y. Role of lysophosphatidylcholine in T-lymphocyte activation: involvement of phospholipase A_2 in signal transduction through protein kinase C. Proc Natl Acad Sci USA 1992;89:6447–51.
[38] Liu YJ. Dendritic cell subsets and lineages, and their functions in innate and adaptive immunity. Cell 2001;106:255–8.
[39] Imler JL, Hoffmann JA. Toll receptors in innate immunity. Trends Cell Biol 2001;11:304–11.
[40] Steinman RM, Turley S, Mellman I, Inaba K. The induction of tolerance by dendritic cells that have captured apoptotic cells. J Exp Med 2000;191:411–6.
[41] Buttke TM, Sandstrom PA. Oxidative stress as a mediator of apoptosis. Immunol Today 1994;15:7–10.
[42] Ashkenazi A, Dixit VM. Death receptors: signaling and modulation. Science 1998;281:1305–8.
[43] Price BE, Rauch J, Shia MA, Walsh MT, Lieberthal W, Gilligan HM, O'Laughlin T, Koh JS, Levine JS. Anti-phospholipid autoantibodies bind to apoptotic, but not viable, thymocytes in a β_2-glycoprotein I-dependent manner. J Immunol 1996;157:2201–8.
[44] Koh JS, Levine JS. Apoptosis and autoimmunity. Curr Opin Nephrol Hypertens 1997;6:259–66.
[45] Chang MK, Bergmark C, Laurila A, Horkko S, Han KH, Friedman P, Dennis EA, Witztum JL. Monoclonal antibodies against oxidized low-density lipoprotein bind to apoptotic cells and inhibit their phagocytosis by elicited macrophages: evidence that oxidation-specific epitopes mediate macrophage recognition. Proc Natl Acad Sci USA 1999;96:6353–8.
[46] Hack CE, Wolbink G-J, Schalkwijk C, Speijer H, Hermens WT, van den Bosch H. A role for secretory phospholipase A_2 and C-reactive protein in the removal of injured cells. Immunol Today 1997;18: 111–5.
[47] Kume N, Ochi H, Nishi E, Gimbrone Jr MA, Kita T. Involvement of protein kinase C-independent mechanisms in endothelial ICAM-1 up-regulation by lysophosphatidylcholine. Ann NY Acad Sci 1995; 748:541–2.
[48] Takahara N, Kashiwagi A, Maegawa H, Shigeta Y. Lysophosphatidylcholine stimulates the expression and production of MCP-1 by human vascular endothelial cells. Metabolism 1996;45:559–64.
[49] Kita T, Kume N, Yokode M, Ishii K, Arai H, Horiuchi H, Moriwaki H, Minami M, Kataoka H, Wakatsuki Y. Oxidized-LDL and atherosclerosis. Role of LOX-1. Ann NY Acad Sci 2000;902:95–100.
[50] Takeshita S, Inoue N, Gao D, Rikitake Y, Kawashima S, Tawa R, Sakurai H, Yokoyama M. Lysophosphatidylcholine enhances superoxide anions production via endothelial NADH/NADPH oxidase. J Atheroscler Thromb 2000;7:238–46.
[51] Cieslik K, Lee C-M, Tang J-L, Wu KK. Transcriptional regulation of endothelial nitric-oxide synthase by an interaction between casein kinase 2 and protein phosphatase 2A. J Biol Chem 1999;274:34669–75.