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REVIEW

Lysophospholipid Receptors in Cell Signaling

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Abstract—There is increasing evidence that different phospholipids are involved in regulation of various cell processes and cell–cell interactions. Lysophospholipids (lysophosphatidic acid, lysophosphatidylcholine) and a number of lysosphingolipids play particular roles in these regulations. Their effects are mediated by specific G-protein-coupled receptors. G-Protein coupled signal transduction to the cell nucleus involving a chain of intracellular protein kinases induces the main effects in cells—growth, proliferation, survival, or apoptosis. This review summarizes recent data on various groups of lysophospholipid receptors and their cell signal transduction pathways.

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Lysophospholipids (lyso-PL) play an important role in intracellular signal transduction. This class of phospholipids contains just one carbon chain: the long chain of sphingosine alcohol (in lysosphingolipids) or one fatty acid (in lysoglycerophospholipids). Structural features of lyso-PLs, large polar heads and one hydrophobic tail, underline their ability to initiate opening of TREK-channels (K^+ channels of central and peripheral nervous system cells) due to their action on channel proteins and/or membranes [1]. Some lyso-PLs also initiate and regulate cell proliferation; mechanisms responsible for these effects share some similarity with the mechanisms mediating polypeptide growth factor effects. There is evidence that lyso-PLs may function as mediators initiating numerous cell effects [2-4].

Diverse effects of lyso-PLs and cell responses include mitogenesis, differentiation, cell migration, and cell viability (anti-apoptosis). Mediator-induced cell effects cause corresponding physiological phenomena: vasoconstriction, wound healing, immunomodulation, angiogenesis, and platelet aggregation. Lyso-PL signal molecules regulate various metabolic reactions acting on such processes as calcium mobilization, adenylyl cyclase inhibition, and mitogen-activated protein kinase (MAPK) activation [2]. In biological membranes, lyso-PL content is extremely low (from 0.5 to 6%).

Lysophosphatidylcholine (LPC) is the best-studied lyso-PL (due to its relatively higher tissue content compared with other lyso-PLs); its regulatory effects have been summarized in many reviews [5, 6]. Other biologically active lyso-PLs including lysophosphatidic acid (LPA), sphingosine-1-phosphate (S1P), and sphingosine phosphocholine (SPC) also attract much interest; they are now considered as important extracellular signaling molecules exhibiting pleiotropic effects on cell metabolism [7]. Studies of these lyso-PLs representing just "microscopic" proportions of the main cellular phospholipids became possible only during the last decade due to the development of highly sensitive method of lipid fractionation and analysis, such as highly effective liquid chromatography with light scattering detector and electrospray mass spectrometry. For example, the amount of LPA is ~154 pmol per cell (compared with 20.4 nmol of phosphatidylcholine) and its content in blood is 0.1-6.3 μmol/liter [8, 9].

Abbreviations: EDG) endothelial differentiation gene; ERK) extracellular signal regulated kinase; GPCR) G-protein coupled receptors; LPA) lysophosphatidic acid; $LPA_{(1-5)}$) LPA receptors; LPC) lysophosphatidylcholine; lyso-PL) lysophospholipids; MAPK) mitogen activated protein kinase; PDGF) platelet derived growth factor; S1P) sphingosine-1-phosphate; SPC) sphingosine phosphocholine; TNF) tumor necrosis factor; VCAM) vascular cell adhesive molecules.

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Lysophosphatidic acid, the product of phospholipase-catalyzed hydrolysis of phospholipids, belongs to a new family of lipid mediators; these are endogenous growth factors that can induce various biological effects [8]. Formation and level of LPA in the cell is regulated by specific signaling processes, controlling acylation/deacylation reactions of phospholipids (including phospholipase and lysophospholipase reactions).

Significant (more than one order of magnitude) increase in blood LPA was found in patients with ovarian carcinoma. Since this increase has been detected at the first stage of this disease, it is suggested that LPA may be used as a new marker of ovarian cancer [9]. LPA also induces proliferation and mitogenic signaling of prostate cancer cells [8]. It is suggested that tumor cells secrete LPA. The concentration of LPA corresponding to that in ascites liquid of ovarian carcinoma indirectly stimulated cell growth by increasing expression of vascular endothelial growth factor. LPA may also employ the other regulatory mechanism; it involves the increase in cyclin D1 content in tumor cells, which stimulates proliferation [10].

Follicular liquid of healthy persons also contains LPA [11]; this suggests that LPA is also involved into normal physiology of ovaries, and it may be locally generated in cells of the reproductive system. It is possible that LPA plays multiple roles in male and female reproductive physiology and pathology [8].

The lipid mediator LPA influences various cell processes. It stimulates migration and proliferation of human carcinoma cells (DLD1), their adhesion to collagen type 1, and secretion of endothelial growth factor and interleukin-8. Physiological concentrations of LPA increase migration, proliferation, adhesion, and secretion of angiogenic factors; this increases metastasizing potential of DLD1 carcinoma cells [12].

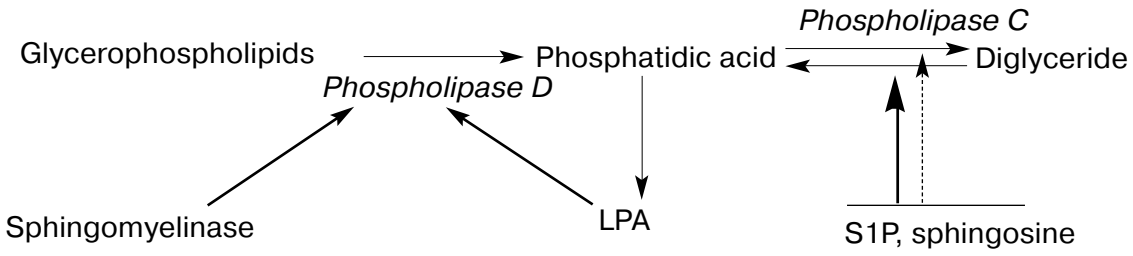
Lysosphingophospholipids—sphingosine-1-phosphate (S1P) and sphingosine phosphocholine (SPC). Biological effects of S1P and SPC have been considered in several reviews [13-17]. These lyso-PLs are key signal molecules involved in stimulation of cell growth. Potential calcium mobilizing agonists, they also induce vasoconstriction of microvessels and coronary arteries.

S1P is involved in regulation of angiogenesis [18] and cerebral vasospasm; it increases proliferation and chemotaxis of endothelial cells [1-13]. Accumulation of S1P results in an increased level of the adhesive molecules E-selectin and VCAM-1 [19]. Some factors, such as TNF-α [20] or platelet aggregation, induce S1P accumulation, and this may account for the major proportion of chemotactic activity of blood serum [21]. SPC increases sensitivity to Ca^{2+} by causing intracellular accumulation of this ion, and SPC can induce endothelium-dependent relaxation of coronary artery; the latter SPC effect is attributed to its activation of NO-synthase [17, 22]. Under conditions of blockade of NO-synthase or its poor susceptibility to SPC (due to unfavorable cell topology of its formation), the relaxing effect of SPC is abolished and replaced by some other effects of this regulator [22].

Interactions between lysoglycero- and lysosphingophospholipids. During biosynthesis of lysoglycero- and lysosphingo-PLs and their signaling, there are certain interactions. Biochemical reactions of biosynthesis, cleavage, and signaling are closely related and coordinated [2] (Scheme).

Reactions of sphingolipid metabolism can generate phosphatidic acid, an LPA precursor; this involves three main mechanisms [23-26]. Glycerophospholipid conversion into phosphatidic acid catalyzed by phospholipase D can be increased by sphingomyelinase, which favors phospholipase cleavage in the membrane, and also by stimulation of phospholipase D activity of LPA [26]. S1P and sphingosine inhibit phosphatidic acid hydrolysis to diacylglycerol catalyzed by phospholipase C; this abolishes protein kinase C stimulation. Intracellular S1P and inositol triphosphate generated by phospholipase C enhance the intracellular concentration of Ca^{2+}. There are both cooperative and antagonistic interactions between LPA and S1P and their signaling processes; these interactions are strictly controlled, and this control is determined by the conditions in cells and the whole organism [26].

Two groups of lysophospholipid effects. Although lyso-PLs act "in one direction" with polypeptide growth factors, lyso-PLs are characterized by a wider spectrum of



Scheme illustrating interaction of lysophospholipid reactions. A plain arrow indicates metabolic reaction, bold and dashed arrows show activation and inhibition effects, respectively

biological activity. Numerous cell effects of lyso-PLs can be separated into two groups depending on the "direction" of the biological effect and mechanisms responsible for manifestation of these effects [2, 27]: i) the growth stimulating effect implies not only direct effect on cell growth, but also various processes related to survival of cells under various conditions; ii) the effect on cytoskeleton proteins, which determine the influence of lyso-PL on cytoskeleton related processes and interactions.

The interactions pooled under the term "growth" effect include prolongation of survival, protection against apoptosis and its inhibition, changes in cell differentiation, and stimulation or inhibition of proliferation [28-30]. Cell proliferation of responses induced by lyso-PLs may also involve several mechanisms (Table 1).

Stimulation of cell proliferation by lyso-PLs may involve at least three pathways [10, 31-36]: initiation of immediate early gene response related to cell growth; production and secretion of polypeptide growth factors (e.g. LPA stimulates keratinocytes by increasing production and secretion of transforming growth factors α and β; this stimulates proliferation and differentiation of cells [31]); stimulation of cell sensitivity to the effects of polypeptide growth factor. This effect appearing at the lowest LPA concentrations is based on the synergistic interaction with the polypeptide. For example, LPA promotes the effect of platelet-derived growth factor (PDGF) on culture of rat mesangial cells [37, 38]. It is also possible that LPA and S1P exhibit an antiproliferative effect [39], which has been demonstrated using melanocytes or hepatic myofibroblasts [40, 41]. This effect is related to the increase in cAMP analogs [41]; this suggests the possibility of an effect of adenylyl cyclase activators, which act in concerted manner with LPA.

Cell response to any treatment influencing growth and proliferation is adequate in the presence of the lowest LPA concentration required for MAPK activation [2, 42].

The effects of LPA related to functional response of cytoskeleton and adhesive proteins of the cell surface are linked to kinase phosphorylation requiring higher level of LPA [43]. This biochemical parameter discriminates two pathways of cell response. This a common group of LPA and S1P functions characterized by various cell manifestations (Table 2) [2].

Table 1. Variants of effects of lysophospholipids (LPA and S1P) on cell proliferation related processes

Stimulation of proliferation	Inhibition of proliferation
Immediate early response of cell growth related genes	Inhibition of proliferation of some cell types realized by activation of adenylyl cyclase and increase in cAMP level
Induction of production and cellular secretion of one or several polypeptide growth factors	
Stimulation of sensitivity of some cell types to polypeptide growth factor	

Table 2. Variants of lyso-PL (LPA and S1P) effects on processes related to influence on cytoskeleton proteins

	Effects of lysophospholipids
1	Influence on cell adhesion and aggregation
2	Change in shape and mobility of cells
3	Effect on secretion of ions and processes related to cell transmembrane endocytosis and exocytosis

One subgroup of these functions is related to the effect on cell adhesion and aggregation. This causes an increase in cell interaction with other cells and with the connective tissue matrix, aggregation of platelets, epithelial and endothelial cells, formation of sites of cell attachment to each other, and assembly of adhesive complexes and fibronectin on the cell surface. Induction of adhesive molecule expression via generation of sphingolipids, particularly S1P [19], can also be referred to this group.

The other subgroup of the "cytoskeleton" effects of lyso-PLs is related to change in shape and motility of cells. This includes contraction of smooth muscles, vasoconstriction, axon constriction, chemotaxis, and cell monolayer invasion. Involvement of S1P and SPC in migration of cells, conditioning of smooth muscle and vascular endothelial cells for chemotaxis, and pro-angiogenic action can also be referred to this subgroup of lyso-PL effects [4, 8, 18-21]. Cell migration involves putative activation of receptors by phospholipase C and tyrosine phosphorylation in p125AK kinase [43]. Calcium signaling (i.e. redistribution of intracellular Ca^{2+} during cell signal transduction induced by lyso-PL receptor interaction) is also crucial [44].

Effects on ion secretion and processes related to cell transmembrane endocytosis and exocytosis [2] represent the third subgroup of lyso-PL functions.

The combination of two types of these effects is also possible [10, 27]. For example, the effect of lyso-PLs on cell and tissue differentiation is related to changes in expression of certain genes in response to growth factors; this is typical for the first subgroup of lyso-PL effects. This effect is also related to the responding activation of surface adhesive proteins; signaling pathways of this effect can be attributed to the second subgroup of actions (which depend on cytoskeleton).

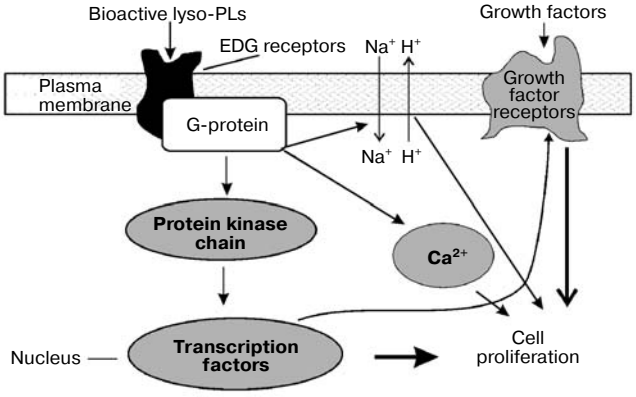
Cell receptors to lysophospholipids. Diversity of lyso-PL effects seriously complicates elucidation of precise mechanisms of their realization. Some authors have postulated involvement of specific receptors in these processes. Indeed, recent use of genomic approaches resulted in identification of such receptors.

LPA and S1P receptors. The first inducible S1P receptor was identified in endothelial cells. It is called the EDG receptor, using the name of the corresponding *EDG* (Endothelium Differentiation Gene) [45]. Extracellular S1P released from platelets or other cells is its physiological ligand. Subsequent studies revealed similar receptors [46]. These receptors are coupled to G-protein, a highly active regulatory plasma membrane heterotrimeric protein involved in control of various transcription processes and membrane permeability [2, 47-49]. Now a whole family of S1P-sensitive receptors known as EDG-1, -3, -5, -6, and -8 has been characterized. These receptors are also defined as G-protein coupled receptors (GPCR) due to their coupling to G-proteins [45, 49]. The mechanism of ligand–receptor interactions employing G-protein is illustrated by the scheme shown by Gouni-Berthold and Sachinidis (figure) [50].

According to this scheme, ligand binding to its receptor can cause conformational changes in this receptor, inducing corresponding response in G-protein. This chain of events influences G-protein regulated processes: change in activity of specific mitogen-activated protein kinases (MAPK and MEK) or nuclear transcription factors or opening of ion channels (i.e. all key processes of living cells). This underlines multiple modes of the effects of lyso-PLs and diversity of cell responses to them, which occur via growth-stimulating and cytoskeleton-dependent pathways.

Eight genes encoding EDG receptors have been identified in the human genome. Five genes encode S1P receptors (EDG-1, -3, -5, -6, and -8), and three others encode LPA receptors (EDG-2, -4, and -7) [4, 49]. The EDG receptors specific to LPA as well as S1P are coupled to G-protein; they have been identified and some of them have been cloned [51].

EDG receptors (encoded by *EDG* genes) have been characterized in terms of amino acid composition and sequence; they contain from 354 to 382 amino acid residues. Systems of regulation of these receptors as well as genes encoding these receptors have also been characterized. Primary structures of some EDG receptors share sites with identical sequences. Although different tissues express different EDG receptors, all of them are coupled to multiple types of G-proteins [2, 49].



Mechanisms of intracellular signaling of lysophospholipids and putative pathways of their effects on cell proliferation [50]

Based on homology of amino acid sequences, two clusters of EDG receptors are recognized. For human EDGs, EDG-2 and EDG-4 exhibiting affinity to LPA share 46% of amino acid sequence homology; EDG-1, EDG-3, and EDG-5 share 45-60% of sequence homology. Homology of proteins from various clusters is much lower and varies within 31-34% [52].

Some individual differences between two homologous clusters of GPCR are in parallel to differences in the receptor affinity to various lyso-PL ligands: EDG-1, -3, and -5 and EDG-2 and -4 mediate most signals from S1P and LPA, respectively [49].

However, in spite of these differences all members of the EDG family share some common structural features. For example, in the first extracellular loop they lack a cysteine residue found in most GPCRs. Each EDG receptor has also characteristic structural elements related to some unknown reactions of ligand binding or signal transduction. This was illustrated by substitution of alanine for proline in the seventh transmembrane domain of EDG-4 [49]. Malignance progression correlates with differential expression of various subtypes of LPA receptors [53]. Normal prostate tissue expresses a special isoform of LPA receptor, EDG-7 [54]. Increased expression of EDG-4 was found in ovarian cancer cells, whereas expression of EDG-2, -4, and -5 was higher in normal ovarian epithelium [47, 55]. The structures of *EDG* genes have not been fully characterized. Mutation in the G-coupled receptor to S1P changed signaling events including mobilization of Ca^{2+} and MAPK activation [47]. The receptors EDG-1 and EDG-3 regulate formation of capillary pathways and their branching. Studies *in vivo* in mice deficient in EDG-1 receptor have shown that S1P receptors are involved in formation of blood vessels and their maturation (angiogenesis) [56]. This phenomenon has also been demonstrated in HUVEC (human umbilical vein endothelial cell) culture [18].

Many effects of LPA and S1P on cells are realized via EDG receptors. However, the particular role of each EDG receptor-mediated signaling in certain types of target cells still requires detailed investigation. Binding of S1P to EDG receptors plays a significant role in Ca^{2+} mobilization, regulation of cell motility, and also in migration and differentiation of endothelial cells. The resulting cell response to the effect of exogenous S1P depends on the type of expressed EDG receptors and involvement of certain signal transduction pathways. In mice, it has been demonstrated that expression of at least one LPA receptor is regulated in brain [57]. LPA and S1P increased expression of plasma membrane bound heparin binding epithelial growth factor (HB-EGF) in T-cells, macrophages, and some other cell types [58].

It should be noted that in some studies EDG receptors have been defined according to nomenclature proposed by the International Pharmacological Committee (IUPHAR), in which they are named by a certain ligand with the index corresponding to EDG number. For example, S1P receptors (EDG-1, -5, -3, -6, and -8) have been named as $S1P_1$, $S1P_2$, $S1P_3$, $S1P_4$, and $S1P_5$, and three LPA receptors (EDG-2, -4, and -7) have been renamed to LPA_1, LPA_2, and LPA_3 [49]. This nomenclature has not yet displaced the former one, which is more convenient in our viewpoint because it cannot confuse receptor with its ligand. Anyway, two nomenclatures are still used in the literature.

SPC and LPC receptors. Besides S1P, all identified S1P receptors of the EDG family (EDG-1, -3, and -5) respond to stimulation by sphingosine phosphocholine (SPC), although this stimulation requires much higher (micromolar) concentrations of SPC compared with (nanomolar) concentrations of S1P [17]. The EDG receptors exhibit low affinity to SPC and may be involved in some of its extracellular effects only at micromolar concentrations of SPC. At the same time, SPC exhibits its own biological effects, which do not depend on S1P. For example, it has been demonstrated that SPC (but not S1P) inhibits Ca^{2+} flux in GH_4C_1 cells, stimulates formation of superoxide anion in HL-60 cells, and stimulates inositol triphosphate in airway epithelial cells. These facts together with the presence of SPC in normal blood plasma [59] indicate the possible existence of other SPC-specific receptors [17].

Recent identification of high affinity GPCR to SPC in ovarian cancer cells supports this hypothesis. This receptor insensitive to S1P [60, 61] known as ORG1 (ovarian cancer GPC-receptor 1) was similar to orphan receptors expressed in placenta, lungs, liver, kidneys, brain, heart, and some cells of the immune system. This receptor is activated by nanomolar concentrations of SPC [60]. Other lyso-LPs (S1P, LPA, LPC) or platelet-activating factor (PAF) did not compete for SPC binding at ORG1. In cells overexpressing ORG1, addition of SPC caused a sharp increase in intracellular Ca^{2+} concentration; this effect was blocked by pertussis toxin (used as a tool for G-protein switch off [48]). The effect was stereospecific, because it was induced by natural D-erythro-SPC but not L-threo-SPC. SPC-induced inhibition of cell growth obviously employed other mechanisms because this effect was insensitive to inhibition by pertussis toxin, and ERK activation promoted its manifestation [60].

Other identified receptors were less specific to SPC, and they also interacted with LPA. These include lymphocyte G2A receptor playing an important role in functioning of these cells [62] and also G PR4 expressed in many tissues. In cells overexpressing G PR4, addition of both SPC and LPA caused increase in intracellular Ca^{2+}, ERK activation, and increased synthesis of DNA; these effects were sensitive to the presence of pertussis toxin, i.e. were realized by G-protein mediated pathways [61].

Thus, SPC is an independent mediator; its structural resemblance to other lysophospholipids (especially S1P) accounts for realization of some of the effects of SPC via S1P-signaling pathways involving EDG receptors (however, this requires higher SPC concentrations) [17, 63]. Table 3 summarizes information on specificity, localization, and biological effects of lyso-PL receptors [17, 27, 28].

Lysophospholipid signal transduction using GPCR. In spite of diversity of cell lyso-PL receptors, there are sev-

Table 3. Cell receptors of lysophospholipids*

Receptors	Ligands (and required concentrations)	Expressing tissues	Biological effect
ORG1	SPC, stereospecific for D-erythro-SPC (nM)*	Placenta, lung, liver, kidney, brain, heart, immune system	Increase in intracellular Ca^{2+}, ERK activation, inhibition of proliferation
G2A	LPC (nM) SPC (nM-μM)	Lymphocytes	Increase in intracellular Ca^{2+}, ERK-activation, stimulation of T-cell migration
GPR4	SPC (nM) LPC (nM)	Ovaries, liver, lung, kidney, immune system, brain	Increase in intracellular Ca^{2+}, ERK-activation, stimulation of proliferation
EDG-1, -3, -5, -6, -8	S1P (nM) SPC (low μM)	Tissues of nervous, cardiovascular, immune, and reproductive systems (including endothelial and smooth muscle cells) and other tissues	"Growth effects": influence on apoptosis, differentiation, and proliferation (see Table 1)
EDG-2, -4, -7	LPA (nM)		Influence on cytoskeleton proteins (see Table 2)

Note: ERK, extracellular signal regulated kinase.
* From [17, 27, 28].

eral common elements involved in signaling pathways. One of these common elements includes the mode of receptor interaction with G-protein. G-Proteins are heterotrimers, which consist of α-, β-, and γ-subunits (G-chains), each of which is responsible for a certain type of interactions and controls one or several biochemically important signaling reactions. GPCR proteins bind to various types of G-chains and therefore realize specific control of certain processes.

Mechanisms of LPA signal transduction involve small GTP-binding proteins, Ras and Rho. These proteins stimulate cell proliferation and initial step of conversions of cytoskeleton proteins (e.g. actin). Their signal transduction is coupled to G-protein and employs MAPK, phospholipase C, and some protein tyrosine kinases. Binding of S1P and LPA to EDG receptor causes G-protein mediated activation of these mitogenic pathways [35, 50, 64]. It is suggested that other lipid messengers may activate Rho kinase using similar mechanism and cause inhibition of the catalytic domain via conformational changes facilitating catalytic site susceptibility [54, 65]. Interaction of EDG-1 with G-protein induces phosphorylation in one of the cytoskeleton proteins (Cas protein); this suggests a possible role of EDG in rearrangement of cytoskeleton proteins and endothelial cell motility [66].

Productive binding of lyso-PLs to more than one receptor can cause many cell responses [2, 17, 49]. Response of receptor to its interaction with a lyso-PL ligand can influence a certain chain of a G-protein accompanied by activation of a certain metabolic pathway coupled to the particular G-protein.

These may include [67-69] activation of phospholipase C followed by phosphoinositide and diacylglycerol regulated Ca^{2+} mobilization and activation of protein kinase C; transcription of a site of the *SRE* gene employing GTP-bound peptide factor (rhoGTP pathway); activation of phospholipase D and phosphoinositol-3-kinase; involvement in cytoskeleton-dependent functions.

Binding of GPCRs with LPA or S1P followed by subsequent coupling to G-protein induces proliferation by initiating synthesis of intermediate transcription protein factors (SRF and TCF). Their production accompanied by nuclear translocation requires activation of both ras- and rho-pathways. Regulatory factors SRF and TCF bind in SRE-assisted manner to specific DNA sites and initiate proliferation and other cell responses [70].

The main effects of lyso-PLs on the cell include stimulation of proliferation, survival related functions, inhibition of apoptosis, effects on differentiation, and a wide spectrum of other responses [2-5, 12, 18]. In some cases (where mechanisms have been clarified), each of these effects could be referred to changes in activity or quantity of one or two cell functional proteins. Many regulatory processes are subjected to complex effects of various lyso-PLs and sphingolipids, which influence ion transport, processes related to apoptosis, etc.

Employing these processes, lyso-PLs, unique mediators of cell growth, differentiation, and activity, are involved (via a complex subfamily of GPCRs) in regulation of expression of biologically important proteins; they influence content and/or activity of these proteins in cells and therefore many cell processes.

The results of the above-mentioned studies provided deeper understanding of new biological roles of lyso-PLs, their interaction with polypeptide growth factors, which in some cases act together with lyso-PLs in realization of many pathways of biochemical signal transduction to the cell nucleus. In practical aspects, these data indicate the possibility of using lysoglycero- and lysosphingolipids for evaluation of the degree of pathological processes followed by subsequent search for their medicinal correction [71].

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